STUDIES IN AROMATIC NITRATION

(Nitration and Acetoxylation with Nitric Acid-Acetic Anhydride)

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ABSTRACT

1,4-Acetoxy-nitro adducts have been isolated from the reactions of o-xylene, p-xylene, hemimellitene and 3-bromo-o-xylene with nitric acid-acetic anhydride mixtures. These have been shown to decompose into acetoxy-substituted aromatics. A cyclohexa-2,5-dienone has been isolated from the reactions of 4-bromo- and 4-acetoxy-o-xylene with nitric acid-acetic anhydride, and this has been shown to decompose into two isomeric nitro-3,4-xylenols. The product distributions from the reactions of mesitylene, pseudocumene, durene, isodurene, prehnitene, pentamethylbenzene, hexamethylbenzene and 3- and 4-deutero-o-xylenes with nitric acid-acetic anhydride have also been determined. These data, and data from earlier work, are discussed in terms of a mechanism involving nitration at a methylated position, to form a carbonium ion which either adds acetate or loses a proton to give a transient methylenecyclohexadiene species.

The kinetics of nitration of mesitylene, m-xylene, o-xylene, toluene and benzene in nitric acid-acetic anhydride-acetic acid have been investigated, either individually or by competition methods. The results are discussed in terms of the possible nitrating species in the system.

INTRODUCTION

A mixture of nitric acid and acetic anhydride has been a common means of nitrating aromatic compounds ever since the method was first used[1] by Orton nearly seventy years ago. It has recently been shown[2] that the nitration of a series of methyl benzenes in this medium is accompanied by significant, and often major, amounts of acetoxylation to give aryl acetates. Thus o-xylene, m-xylene, toluene, pseudocumene, hemimellitene, indan and tetralin were shown to produce aryl acetates in yields ranging from 1% to 51%. Peculiarly, these cases seem to be very nearly the only ones reported in which acetoxy substitution accompanies nitration in this medium (although 1-methylnaphthalene is reported[3] to give an unspecified amount of an acetoxy derivative), in spite of the fact that it has been used for the nitration of many substances spanning a wide range of reactivities. It must be said, however, that many workers have used the method simply as a means of preparing nitro-substituted aromatic compounds, and have thus used methods of isolating their products which would probably leave undetected any aryl acetates present. It is noticeable in some cases that quite low yields of nitro-compounds were obtained[4], suggesting that some acetoxy-compounds may have been formed, but not isolated.

The purpose of this thesis has been to elucidate the mechanism of the acetoxylation reaction. The nature of the nitrating agent in the nitric acid-acetic anhydride system has also been studied.

Suggested mechanisms of acetoxylation

The workers who first observed and studied the reaction considered acetoxylation to be an electrophilic attack on the aromatic ring by protonated acetyl nitrate, an attack which has a high Hammett ρ value, and considerable steric hindrance. This conclusion was drawn from the product distributions obtained, and from a study of the kinetics of the simultaneous nitration and acetoxylation of o-xylene. The proportion of acetoxylation relative to nitration increases as the reactivity of the substrate towards electrophilic attack increases. Thus benzene gives no acetoxy product, toluene gives 3% p-acetoxy product, and o-xylene gives 51% of the 4-acetoxy derivative. This was taken to indicate an electrophilic acetoxylating species. It is also noticeable that the ring positions which are more highly hindered by methyl groups give less acetoxy product than unhindered positions, even though the unhindered positions may normally be the less reactive. o-Xylene, for example, with two ring positions almost equally activated for electrophilic attack, gives acetoxy

products only in the unhindered 4-position, not in the 3-position which is flanked by a "buttressed" methyl group[5]. Similarly, in hemimellitene the 4-positions are more activated but also more hindered (by a "double-buttressed" methyl group) than the 5-position; the 5-position gives 35% acetoxy product, and each 4-position only 5%. These facts were explained by postulating the bulky electrophile, protonated acetyl nitrate. A kinetic investigation[6] of the reaction supported this view. It showed that both the acetoxylation and nitration reactions of o-xylene were zeroth order in hydrocarbon, that the ratio of the rates of acetoxylation and nitration was constant during the reaction, and independent of additives (acetic acid, sulphuric acid and lithium nitrate) which led to a wide range of rates of the overall reaction, and that the reaction was accelerated by small quantities of sulphuric acid or acetic acid, and decelerated by small quantities of lithium nitrate. These results support protonated acetyl nitrate as the attacking species, since the constancy of the relative rates of acetoxylation and nitration requires a common acetoxylating and nitrating agent (or a common precursor), and the great acceleration produced by sulphuric acid points to a protonated species. Since nitric acid in an excess of acetic anhydride exists almost entirely as acetyl nitrate (see p.18), the obvious electrophile is protonated

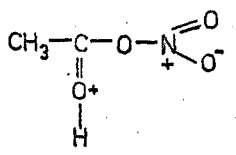
acetyl nitrate, and indeed this appears to be the only one which fits all the requirements. If the rate-determining step were the formation of protonated acetyl nitrate, the reaction would be zeroth order in hydrocarbon, as observed. The mechanism proposed was thus:

$$HNO_3 + Ac_2O \rightleftharpoons HOAc + AcONO_2$$

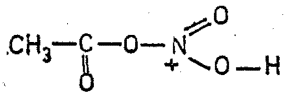
$$AcONO_2 + HA \rightleftharpoons AcONO_2H^+ + A^- \quad \text{(slow)}$$

$$AcONO_2H^+ + ArH \rightarrow ArOAc + ArNO_2.$$

There are three possible protonated acetyl nitrates (I-III) since there are three oxygens which may be protonated on acetyl nitrate. It was considered[7] that III was the most likely attacking entity, since it should be the slowest forming (thus giving the observed rate dependence), and attack by the central oxygen atom would lead to the observed greater steric hindrance to acetoxylation than to nitration.



I



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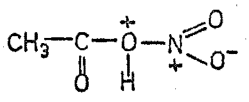
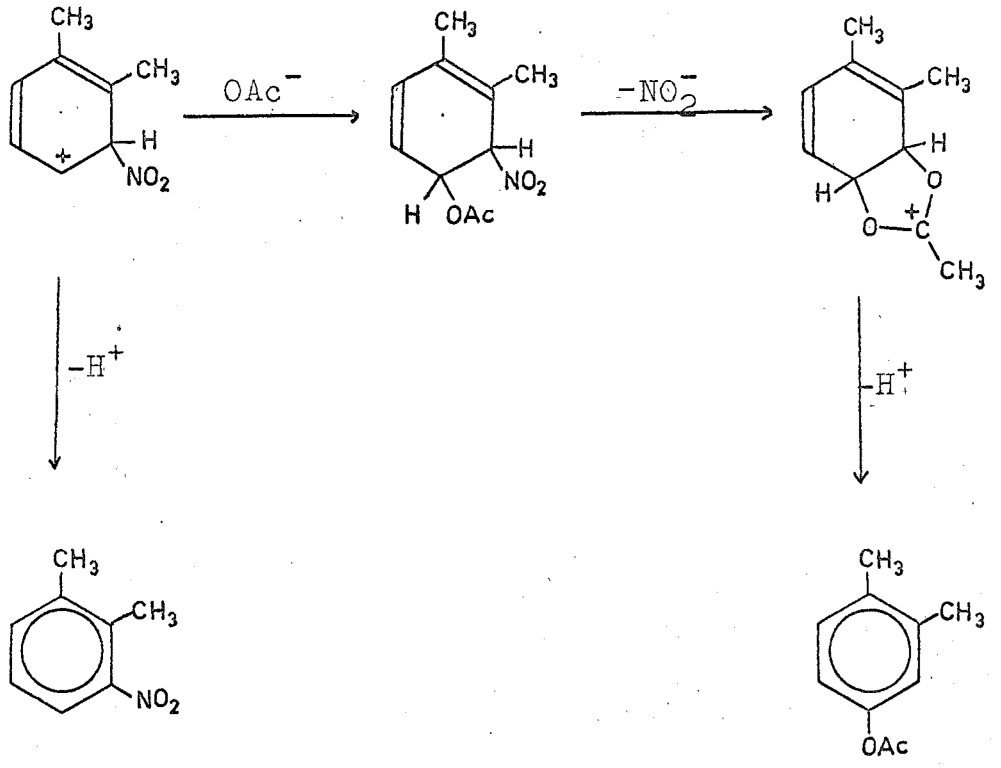


III

Recently a possible reinterpretation of these results was put forward[8]. There is a close similarity between the relative rates and product distributions in nitration by nitric acid in acetic anhydride, and by nitric acid in other organic solvents like nitromethane and acetic acid. This suggests a common nitrating agent in these systems, and it is evident that this cannot be protonated acetyl nitrate. For this reason, an addition-elimination pathway for acetoxylation, not necessarily involving protonated acetyl nitrate, has been put forward[8a].

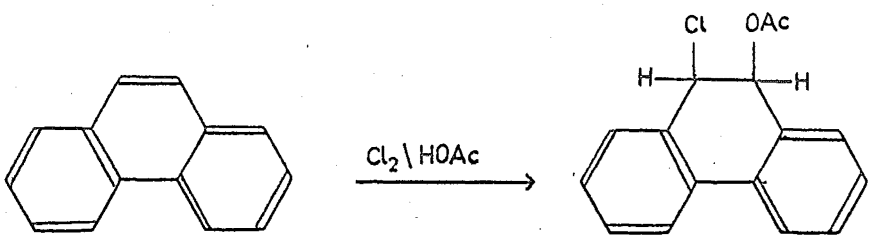


Such a mechanism can also explain the experimentally observed features of the reaction. The two mechanisms are kinetically indistinguishable because the slow step is formation of the reactive species, which leads to zeroth order kinetics in either case. In the addition-elimination mechanism the constancy of relative rates of nitration and acetoxylation is observed because both products come from a single intermediate, and the absence of acetoxylation ortho to the methyl groups could be explained by the lower acidity of the corresponding hydrogen atoms in the acetoxonium ion. Some support for such a scheme comes from the isolation of 9-acetoxy-9,10-dihydroanthracene[9], and 9-acetoxy-10-nitro-9, 10-dihydroanthracene[10] from the nitration of anthracene in acetic acid, and from the known ease with which acetyl nitrate (nitric acid-acetic anhydride) adds to olefinic double bonds[11].

Some features of the reaction are not adequately explained by either mechanism. In particular, neither gives a satisfactory answer to the question of the specificity of the reaction. This specificity is such that even substrates like anisole, which fall into the same range of reactivity as the methyl benzenes studied, fail to give any acetoxy products.

Acetoxy adducts in chlorination

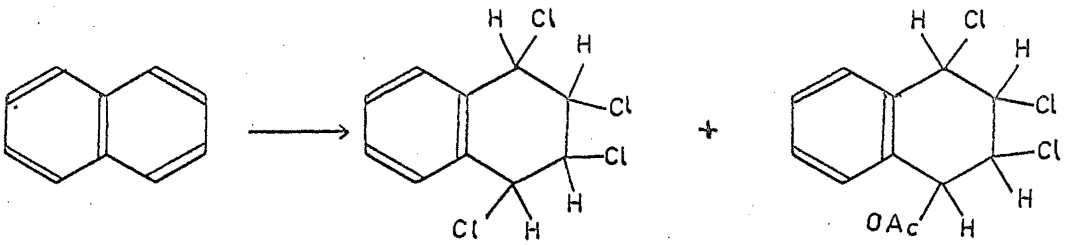
In view of the possibility of an addition-elimination sequence giving acetoxylation in the nitric acid-acetic anhydride system, it is of interest that acetoxy-chloride adducts have been isolated from the reactions of several aromatic substances with chlorine in acetic acid. Thus phenanthrene in this system gives rise[8b] to 9-acetoxy-10-chloro-9,10-dihydrophenanthrene as one product, predominantly as the trans isomer although some cis isomer is also formed. This adduct on heating decomposes into a mixture of 9-chlorophenanthrene and 9-acetoxyphenanthrene.



Bromination in acetic acid gives[12] 9-bromo- and 9-acetoxy-phenanthrenes, though the adduct in this case has not been isolated.

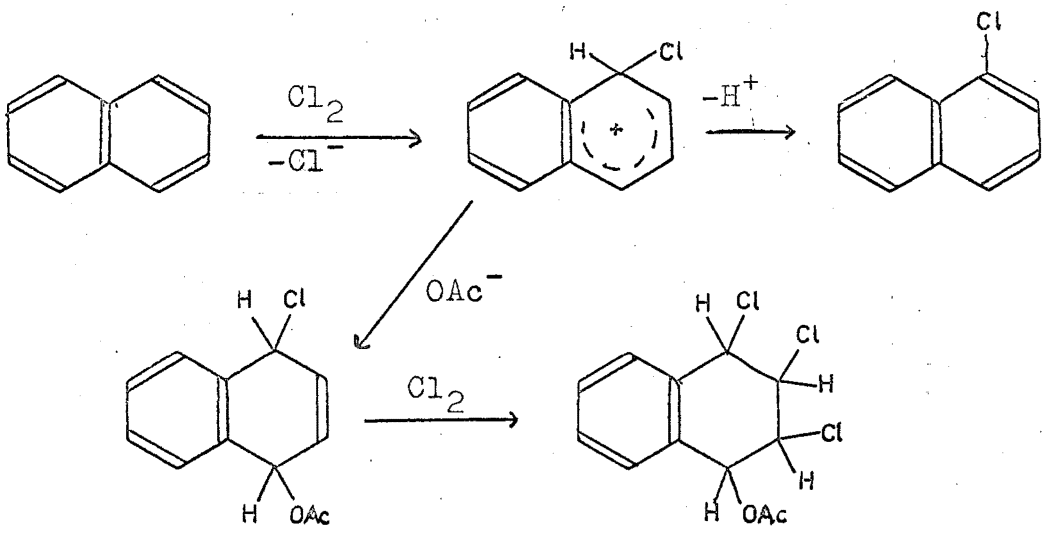
Similar adducts are given by naphthalene[13], biphenyl[14] and some substituted biphenyls[15], fluorene[16], tetrahydropyrene and diphenylmethane[17] and triphenylene[18]. In these cases, however, two addition

steps occur, and the products are acetoxy-trichloride adducts, along with tetrachloride adducts. Naphthalene, for example, reacts by the pathway given below.



(4 isomers) (1 isomer)

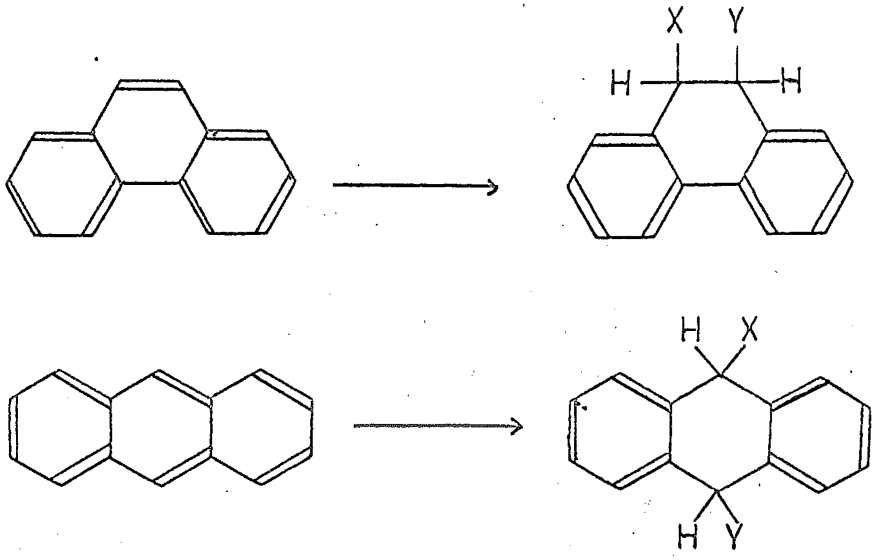
It was concluded that the addition and substitution products in these reactions arise in competition with one another from the same carbonium ion intermediates, which can either lose a proton to give the normal products of substitution, or capture a nucleophile to give the products of addition. Thus one possible route to the acetoxy adduct from naphthalene is



Addition-elimination reactions in aromatic chemistry

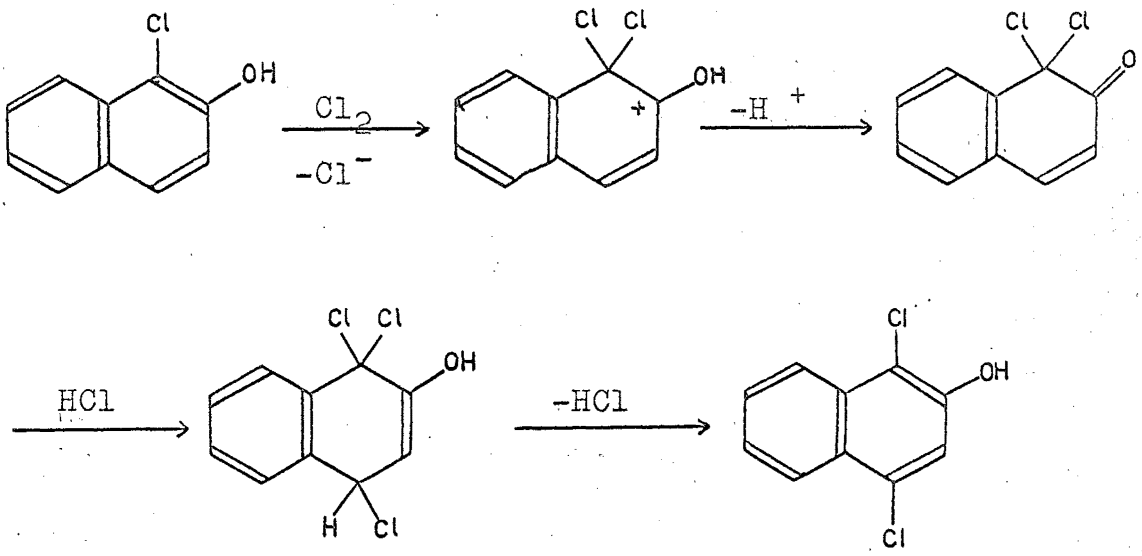
Addition-elimination represents one of the earlier mechanistic formulations of the aromatic substitution reaction[19]. As a generally applicable mechanism it has since been discarded, but there remain a number of reactions for which the operation of such a pathway has been demonstrated.

Many of these reactions arise with polycyclic aromatic compounds. Some instances of adduct formation concurrent with electrophilic substitution for naphthalene, phenanthrene and anthracene have already been given, and many more are known[20], particularly accompanying halogenation. Anthracene and phenanthrene, in particular, will readily undergo addition reactions across the 9 and 10 positions to give products that will decompose by elimination to 9-substituted derivatives.



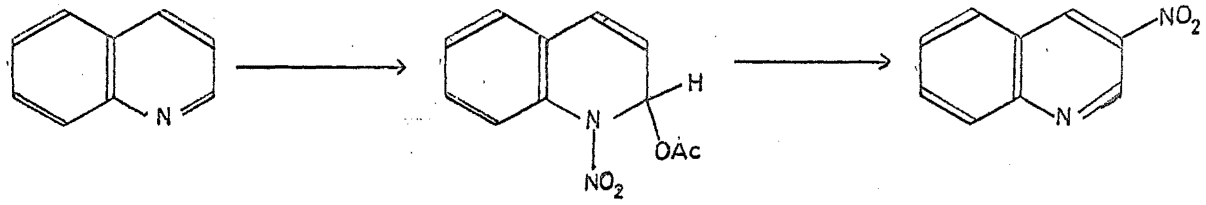
(X = Br, Cl, NO_2; Y = OAc, OMe)

Besides cases like these where adducts have been isolated, there are instances of anomalous orientations accompanying substitution, for which addition-elimination sequences with intermediates too unstable to isolate have been proposed. For example, the formation of 1,4-dichloro-2-naphthol from chlorine and 2-naphthol, when a direct electrophilic substitution would be expected to give 1,6-dichloro-2-naphthol, has been interpreted[21] in terms of the scheme below.



Some substitution reactions of quinoline also result in anomalous orientation, including nitration by acetyl nitrate[22]. It has been suggested that the 3-substituted product, which is not expected from direct electrophilic

attack, comes from preliminary addition, with the addition product undergoing further substitution in the 3-position.

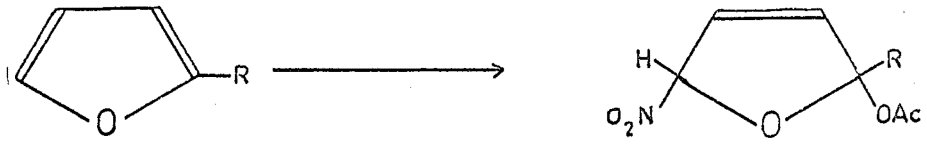


A 1,4 adduct has also been suggested[23].

It is not surprising that addition should be relatively more favourable with these polycyclic molecules than with simple benzene derivatives, since the accompanying loss of resonance stabilization energy is appreciably less in the case of polycyclic compounds. The stabilization energies, determined by heats of combustion, for benzene, naphthalene, anthracene and phenanthrene are, respectively, 36, 61, 83.5 and 91 kcal/mole[20]. Thus the formation of a 1,2 adduct by benzene (which would be analogous to butadiene which has a stabilization energy of 3 kcal/mole) would result in the loss of 33 kcal/mole of resonance energy. The corresponding 1,2 addition to naphthalene would result in the formation of an isolated benzene ring, with additional styrene-like conjugation from the double bond providing an additional 2 kcal/mole of stabilization energy. Thus only 23 kcal/mole of resonance energy would be lost. Similarly, addition across the 9, 10 bond of either

phenanthrene or anthracene would result in the formation of two isolated benzene rings, and loss of only 19 and 11.5 kcal/mole respectively.

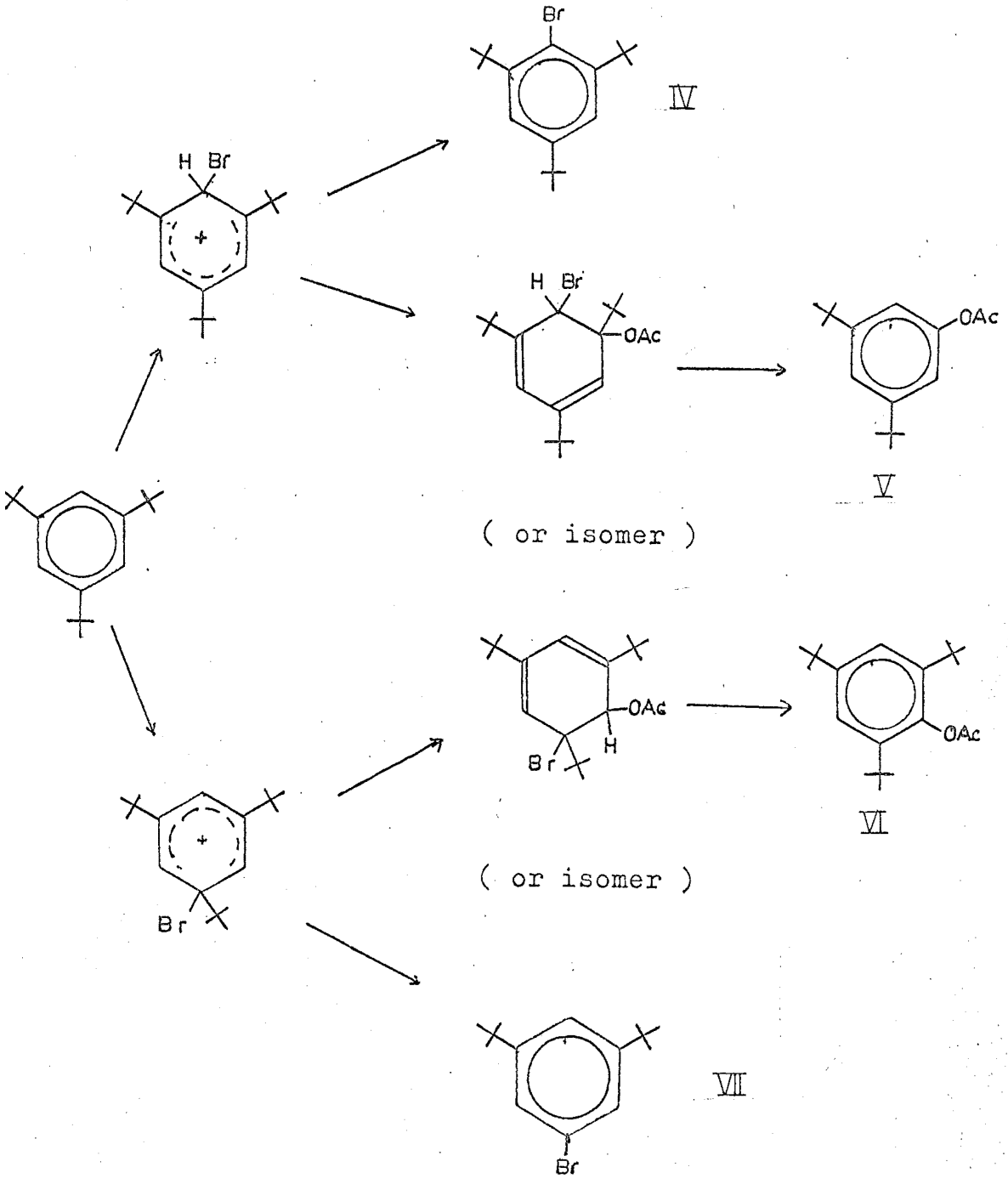
Relatively stable addition compounds have been isolated[24] from the reactions of furan derivatives with nitric acid-acetic anhydride.



However, the degree of aromaticity of furan is known to be considerably less than that of benzene (calculations[25] of the aromatic ring current give furan an aromaticity of 0.6 relative to benzene), and in general such addition reactions occur quite frequently[26]. This reaction, and related less common additions to thiophen, are not, therefore, strictly analogous to additions to benzene systems.

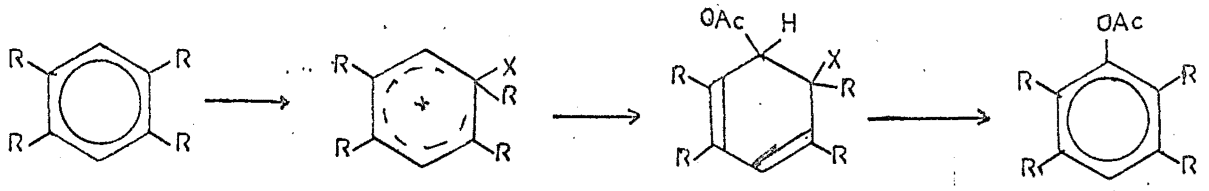
Examples of electrophilic addition-elimination reactions involving an isolated benzene ring are more rare. The formation of adducts during the chlorination of biphenyl and diphenylmethane has already been discussed, and in recent years several other unusual reactions have been explained in terms of addition-elimination sequences. One

of these is the acetoxylation accompanying bromination of 1,3,5-tri-t-butylbenzene in acetic acid[27]. The products of this reaction (IV-VII) are considered to arise as shown in the scheme below.

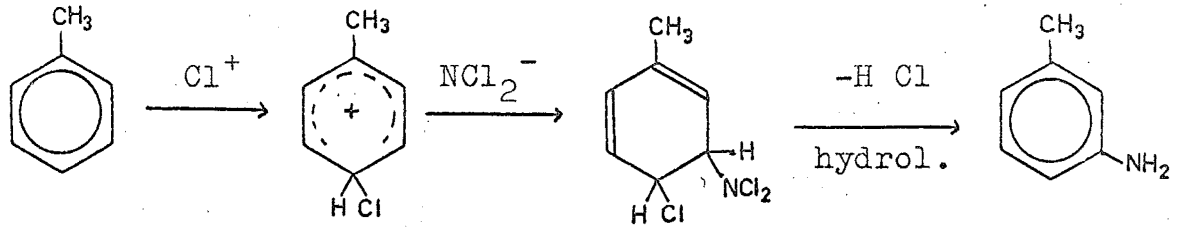


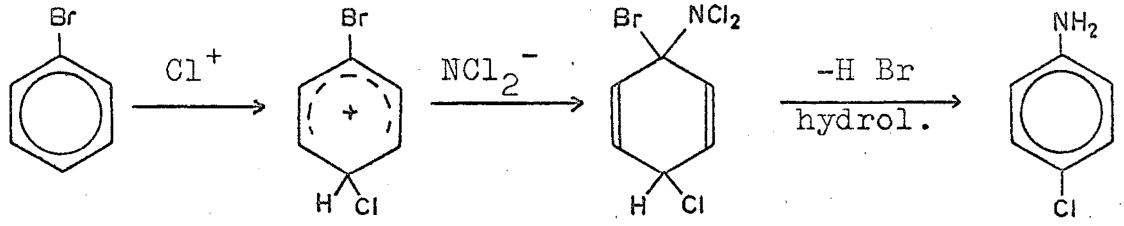
The marked dependence of the yield of aryl acetate products on the amount of added sodium acetate is considered to point to a two step process in which the relative yield of aryl acetate and aryl halide depends upon the rate at which a common intermediate reacts with acetate ions.

This may be a special case because of the constricted nature of the molecule, which means that the rate of proton loss from the initially formed σ-complex is relatively slow and thus addition can compete favourably. It has been shown[28] that the nitration and bromination of 1,3,5-tri-t-butylbenzene proceeds with a rate-determining proton loss. However, substantial quantities of aryl acetates were also obtained from durene and 2,5-diisopropyl-p-xylene which do not show a rate-determining proton transfer on halogenation. In this case the formation of acetoxy products was attributed to electrophilic attack at an alkylated carbon atom to give σ-complexes which could not rearomatize by proton loss, and which instead added an acetate group.



Another reaction for which there is a considerable amount of evidence in favour of an addition-elimination sequence is amination by chloramine and aluminium chloride[29]. The anomalous orientation of the products (m-substitution of alkyl benzenes), the correspondence between the rates of amination and the rates of other electrophilic attacks (which indicates that initial electrophilic attack is involved), the apparent necessity for a ring hydrogen ortho or para to the position of electrophilic attack, and the loss of halogen which attends the reaction when applied to halobenzenes, all point to the mechanism outlined below for toluene and bromobenzene.

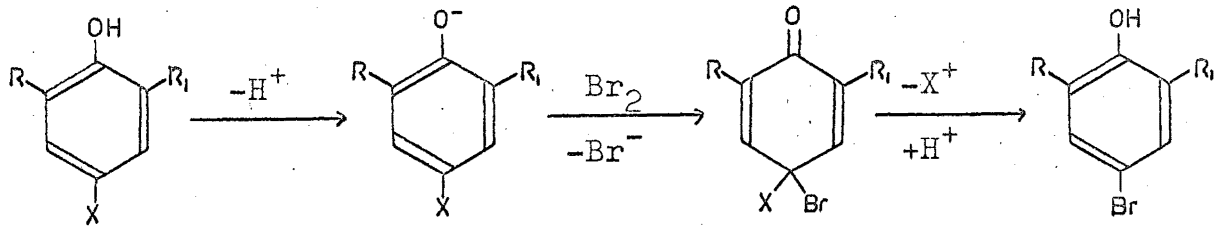




Moreover, in this case the addition products come from a σ-complex which is not "blocked" in any way, and from which proton loss should therefore be rapid.

There are a few other cases[30] of possible addition-elimination mechanisms in the literature; these are sometimes rather speculative.

Some mention should also be made of the formation of dienone intermediates in many electrophilic substitution reactions of polysubstituted phenols[31]. For example, kinetic measurements, studies of the kinetic isotope effect, and u.v. and N.m.r. spectroscopy have established the following mechanism for the bromination of many phenols.



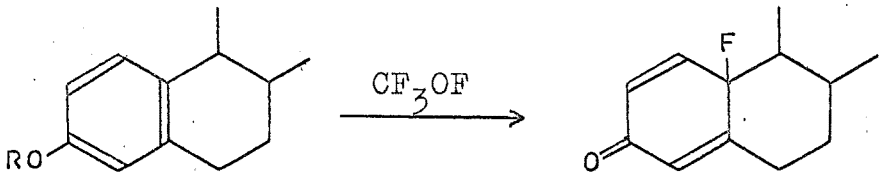
(X = alkyl, halogen, H, NO_2)

When the group X is not easily lost, the dienone can be isolated. 2,4-dienone intermediates are also possible.

These are not addition processes, since no nucleophilic attack is involved as a second step. They are noted here briefly because, like addition-elimination, they require the formation of a diene-type intermediate with

consequent loss of the resonance energy of the benzene ring.

Other reactions of phenols which involve the formation of a dienone (either 2,5 or 2,4) include[31] alkylation, halomethylation under Reimer-Tiemann reaction conditions, electrophilic oxidations by lead tetra-acetate or peroxy acids, and nitration by nitric acid, alone or in acetic acid. Dienones can also be formed from similar reactions of acetoxy and alkoxy substituted aromatic compounds; an example from the steroid field is given[32].



(R = Me, Ac)

As De la Mare has recently pointed out[33], mechanisms such as those described may be more common than this brief survey suggests. The majority of the examples which have been noted are either ones in which adducts have been isolated, or in which abnormal products or orientations have prompted further investigations. Such indications of an addition-elimination mechanism may not, of course, always be present. The intrusion of this type of route may

be very difficult to detect if the addition compounds are unstable under the conditions of the reaction, and especially if they decompose into the same products which are formed, or expected to be formed, by direct electrophilic substitution. This situation does, in fact, occur in the chlorination of phenanthrene[8b], where the dichloro adduct decomposes to give 9-chlorophenanthrene.

The reactive species in nitric acid-acetic anhydride

Nitric acid and acetic anhydride react together at room temperature to give acetyl nitrate.

$$HNO_3 + Ac_2O \rightleftharpoons AcONO_2 + HOAc$$

Physical evidence for this equilibrium comes from vapour pressure measurements[34], Raman spectra[35], freezing point measurements[36], viscosity, density and refractive index measurements[37], and N.m.r. studies[38], all of which have been, or could be, interpreted in terms of the formation of acetyl nitrate. There is also chemical evidence. Bordwell and Garbisch found[11] that if nitric acid and acetic anhydride were mixed at -15°, there was no sign of reaction during mixing, and nitric acid could be recovered almost quantitatively from the mixture by precipitation as urea nitrate, whereas if the reactants were mixed at 25°, an exothermic

reaction ensued and only 30-35% of the nitric acid (and only 22% after one hour's standing) could be precipitated as urea nitrate. The solution mixed at -15° was ineffective as a nitrating agent for alkenes, while that mixed at 25° would nitrate alkenes readily. This was interpreted in terms of formation of acetyl nitrate at room temperature, but not at -15°.

On the basis of this evidence it is generally accepted that in nitric acid-acetic anhydride mixtures with mole fractions of nitric acid below 0.5, the acid is largely converted to acetyl nitrate. It is, however, still uncertain what the actual nitrating species in the system is; some writers favour the nitronium ion, and others one of the protonated forms of acetyl nitrate. The major lines of evidence in favour of these two entities are summarized below.

Bordwell and Garbisch studied the nitration of simple alkenes[11] and several arylalkenes[39] with nitric acid-acetic anhydride mixtures. Their evidence for the formation of acetyl nitrate has already been outlined, and they also showed that the β-nitroacetates, which are the main products of the reaction with alkenes, are formed predominantly by cis addition. Acetyl nitrate, or protonated acetyl nitrate, are the only reasonable attacking species which could give stereospecific addition. The catalysis by added sulphuric

acid, and the anticatalysis by acetate, led to the conclusion that protonated acetyl nitrate was the effective reagent, formed, in the absence of added acid, by the equilibrium

$$AcONO_2 + HOAc \rightleftharpoons AcONO_2H^+ + OAc^-$$

The catalytic effects noted can also be reconciled with a nitronium ion mechanism, but the stereospecific addition is strong evidence that attack on olefins is by protonated acetyl nitrate. However, this does not mean that this species is the effective electrophile in aromatic substitution.

The work of Fischer et al on acetoxylation and nitration in this system has already been surveyed, and their evidence for protonated acetyl nitrate as the reactive species discussed. If, however, the addition-elimination sequence proposed for acetoxylation proves to be the correct one, their observations can also be explained by a nitronium ion mechanism for the nitration process.

The observation of Olah, Kuhn and co-workers[40] on nitration by nitronium salts in sulpholan or nitromethane also has some bearing on the mechanism of nitration in acetic anhydride. These workers showed that in competitive nitrations with nitronium salts, relative reactivities of aromatic compounds were very different from those for

nitrations by nitric acid in organic solvents. Thus for nitration by nitronium tetrafluoroborate in sulpholan, the reactivity of toluene relative to benzene was found to be 1.6 - 1.8, while the corresponding range of figures for nitration by nitric acid in organic solvents (including acetic anhydride) was 21 - 27. Because the low substrate selectivity of nitronium salt nitrations was also observed with other systems such as 75% mixed acid in sulpholan or acetic acid in which the presence of NO_2^+ could be detected spectroscopically, Olah suggested that low selectivity was characteristic of the nitronium ion. This implies that nitration by nitric acid in organic solvents must be due to less reactive electrophiles such as the nitric acidium ion, or, in acetic anhydride, protonated acetyl nitrate.

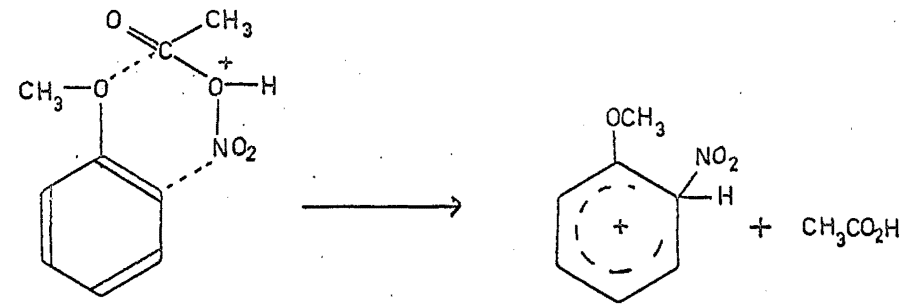
Olah's results, however, have been the subject of some controversy. It is possible that the low relative reactivities observed by him are a consequence of partial mixing control of the reaction rates in these very fast reactions - the rate of reaction being comparable to, or faster than, the rate of mixing - so that the results have no bearing on the mechanism of nitration. This objection has been raised several times[8a,41]. Olah has replied[42] with several counter-arguments. Very recently, however,

Ridd has shown conclusively[43] by the nitration of bibenzyl with nitronium tetrafluoroborate that mixing control is a major factor in this medium; in all cases there was much more dinitrobibenzyl than would be expected if mixing control were not a factor.

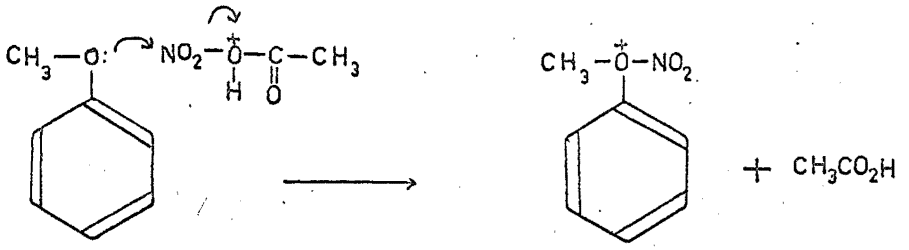
It seems, therefore, that low relative rates cannot be used as an indication of the selectivity of the nitronium ion, and that, conversely, the high relative rates observed with nitric acid in acetic anhydride do not necessarily rule out the nitronium ion as the reactive species.

The anomalously high ortho:para ratios obtained in the nitration of some substrates by nitric acid in acetic anhydride have also been used as evidence that protonated acetyl nitrate is the reactive species. The reactions of anisole, acetanilide, and methylphenethyl ether[44,45], for example, with nitric acid-acetic anhydride give ortho:para ratios of 1.8-2.5, whereas reactions with mixed acid, or with nitric acid alone give ortho:para ratios of 0.25-0.7. In contrast, the reactions of other substrates (e.g. toluene or t-butylbenzene) give closely similar ortho:para ratios with all nitrating systems. It appears that the necessary structural feature for this kind of orientational change, which also occurs on nitration with other acyl nitrates, or with N_2O_5, in organic solvents, is a lone pair of electrons on the substituent near to the ring. It has

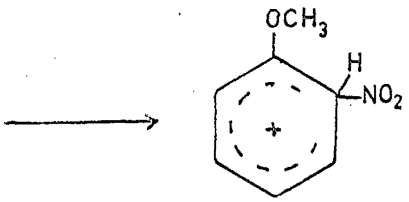
been proposed that this lone pair provides a site for initial reaction, followed by migration to the nearest position (the ortho position) on the ring. Two mechanisms have been suggested (equations (1)[46] and (2)[7,45])



(1)



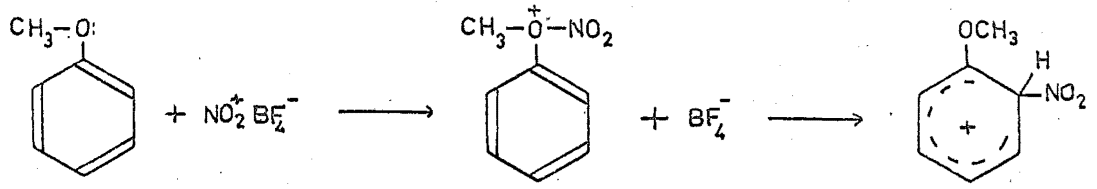
(2)



This mode of specific ortho attack must operate in conjunction with normal nitration, which may still involve NO_2^+ attack[47].

It has also been suggested[8a], however, that such lone pairs are more extensively hydrogen-bonded in the more acidic media involving molecular nitric acid than in acetic anhydride. Such hydrogen-bonding would decrease the

extent of reaction at the substituent and could give rise to the observed changes in orientation. Thus it is possible the nitronium ion is the nitrating agent in acetic anhydride, particularly since high ortho:para ratios have also been obtained[47,48] in reactions with nitronium tetrafluoroborate. With this reagent they have been ascribed to an S_N2-type displacement of BF_4^- from an ion-pair, similar to that outlined for protonated acetyl nitrate.



In the case of nitric acid-acetic anhydride such a displacement could occur from a nitronium ion-solvent complex[3].

Recent work[49] by Schofield et al on the kinetics of nitration by nitric acid in sulphuric acid, perchloric acid, sulpholan and nitromethane has implications about the mechanism in acetic anhydride. They found that in these solvents a limiting maximum rate of nitration was reached, beyond which an increase in the reactivity of the substrate did not produce a corresponding increase in the reaction rate. In sulphuric acid and in perchloric acid the limiting rate was reached at about the level of reactivity represented by toluene, and in the other solvents, at about

that of m-xylene. This was interpreted in terms of the following reaction scheme:

$$HNO_3 + H^+ \underset{k_1}{\overset{k_2}{\rightleftharpoons}} NO_2^+ + H_2O$$

$$NO_2^+ + ArH \underset{k_3}{\overset{k_4}{\rightleftharpoons}} \text{e.p.}$$

$$\text{e.p.} \xrightarrow{k_5} \text{products}$$

The second step, formation of an "encounter pair" (e.p.) can be rate-determining. This leads to an expression for the observed first order rate constant $k_1(obs)$

$$k_1(obs) = \left[NO_2^+\right] \frac{k_3 k_5}{k_4 + k_5}$$

For sufficiently reactive substrates (k_5 large) the rate is therefore determined only by the concentration of nitronium ions, and by k_3 (which, to a first approximation is governed only by the viscosity of the medium), and so reaches a limiting value.

Since the viscosity of acetic anhydride is not markedly different from those of Schofield's solvents, encounter control would also be expected in acetic anhydride, if nitration occurred via the nitronium ion. However, some very high values of relative rates have been reported[50] for nitrations in acetic anhydride by Dewar et al. For

example, anthanthrene was 116,000, and diphenylamine 738,000 times as reactive as benzene, at 0°. This would indicate that the nitronium ion cannot be the electrophile in these cases. However, it is possible that in Dewar's studies, nitration of the very reactive substrates may have been effected through nitrosation, since it has been shown[49] that anthanthrene is very susceptible to this mode of attack, and the nitric acid used by Dewar probably contained a relatively high proportion of nitrous species. Until this possibility has been eliminated, therefore, Schofield's work does not necessarily rule out the nitronium ion as the electrophile in nitric acid-acetic anhydride.

Some support for protonated acetyl nitrate rather than NO_2^+ comes from recent theoretical calculations[51]. Comparison of the heats of formation of the three possible protonated acetyl nitrates, and of the nitronium ion led to the conclusion that NO_2^+ can be ruled out as an intermediate, since its formation from protonated acetyl nitrate should be endothermic by 23.3 kcal/mole. Protonation of the carbonyl oxygen, or the central ether oxygen of acetyl nitrate was predicted to be almost equally likely, and one of these two species was considered to be the reactive entity.

The above provides a summary of the evidence which has been put forward for nitration by protonated acetyl nitrate

in this medium. However, as has been indicated, most of the evidence can still, with certain assumptions, be interpreted in terms of a nitronium ion mechanism. Moreover, as Ridd has pointed out[8a], there is a sufficiently close similarity between the orientation and partial rate factors for nitrations of a number of compounds in acetic anhydride, and in other solvents for which a nitronium ion mechanism is accepted, to suggest a common nitrating agent. Thus it is still not certain which of the two species is the nitrating agent. The argument is, perhaps, rather an academic one, since the difference between protonated acetyl nitrate, and a nitronium ion solvated by acetic acid, would not be very great.

EXPERIMENTAL

Instruments

N.m.r. spectra were run on a Varian A60 machine in CCl_4 or $CDCl_3$ solution, using TMS as an internal standard, unless otherwise noted. Infrared spectra were carried out on a Perkin-Elmer 337 Grating spectrometer, as liquid films, nujol mulls, KBr discs, or in CCl_4 solution. U.v. spectra were measured on a Shimadzu MPS-50L spectrometer in cyclohexane solution. Mass spectra were obtained on an MS902 mass spectrometer. Gas chromatography was carried out on a Varian Aerograph Model 1200; peak areas were either measured with a Kent Chromalog Integrator or estimated as the product of height and the width at half height. The column used most often for gas chromatography was a 6 ft x $\frac{1}{8}$" 3% FFAP on Chromosorb G column. This proved satisfactory for the majority of analyses. Other columns used included PDEAS (3% on Aeropak 30), PEGA (2½% on Aeropak 30), SE-30 (3% on Aeropak 30) and MBM (a capilliary column, 200 ft x 0.01" , used with a stream-splitter). Preparative scale gas chromatography was carried out on an Aerograph Autoprep Model 705.

Reagents

Acetic anhydride (Reidel de Haen A.G.) and acetic acid (B.D.H. Analar) were used without further purification.

Nitric acid (B.D.H.), density = 1.52, was distilled from a mixture of concentrated sulphuric acid (2 volumes) and nitric acid (one volume) at room temperature and 1 mm pressure, after the method of Wright[7]. It was stored at dry ice temperatures. Nitric acid prepared in this way has less than 0.01 mole per cent nitrous acid, and can be stored for several weeks without significant decomposition[52].

Alumina for column chromatography was P. Spence, Grade H, deactivated by adding either 5% or 10% by weight of 10% aqueous acetic acid. Silica gel for column chromatography was Crosfield's "Sorbsil" Grade B.S.S.

Solvents for column chromatography were technical grade. Benzene and light petroleum were distilled off P_2O_5, and ether was used without further purification. Light petroleum refers to the fraction with B.P. 50-70°.

Commercial samples of the aromatic substrates were checked for purity by g.l.c. under conditions which separated them from their isomers and in most cases it was found that further purification was unnecessary. Thus o-xylene (Hopkin and Williams), p-xylene (Phillips Petroleum), m-xylene (B.D.H.), toluene (B.D.H.), benzene (B.D.H.), mesitylene (B.D.H.), hemimellitene (L. Light and Co.), pseudocumene (L. Light and Co.), prehnitene (K and K), durene (B.D.H.), hexamethylbenzene (Koch-Light) and 3-bromo-o-xylene (Aldrich and Co.) were all >99% pure.

Isodurene (Koch-light) contained about 3% of the other tetramethylbenzene isomers, but was used without further purification. Pentamethylbenzene (Koch-Light) containing 6-8% impurity was recrystallized twice from ethanol. This gave crystals better than 99% pure. 4-Bromo-o-xylene (Aldrich and Co.) contained about 15% of the 3-bromo isomer. Distillation through a 24" Nester-Faust annular teflon spinning band produced a material containing only 1-2% of 3-bromo-o-xylene.

3- and 4-deutero-o-xylenes were prepared by decomposing with D_2O the Grignard reagents formed from 3- or 4-bromo-o-xylenes. The appropriate bromo-o-xylene (20 gm, 0.108 mole) dissolved in dry THF (60 ml) was added to magnesium (2.67 gm, 0.110 moles) over a period of one hour, under a nitrogen atmosphere and with stirring. The reaction was stirred for another hour, and D_2O (2.5 mls) added slowly with stirring and cooling. After overnight standing the mixture was poured into water and extracted with ether. The ether and THF were removed by distillation through a spinning band distillation column, and the deuterated o-xylene left was redistilled before use. Both the deuterated compounds showed more than 99% incorporation of deuterium by mass spectrometry.

4-acetoxy-o-xylene was prepared from 3,4-xylenol and acetic anhydride[53]. It had B.P. 95°/5 mm (lit.[54] 235°/760 mm).

General Nitration Procedure

(a) Analytical runs. One of two methods was followed. Except where noted in the results section, the same product distributions, to within a few per cent, were given with each method.

In the first method, the hydrocarbon (0.5 gm) was dissolved in acetic anhydride (1 ml), and cooled in ice-water. Nitric acid (0.1 ml) dissolved in acetic anhydride (1 ml) was run in dropwise with stirring. After 1½ hours the reaction was quenched in water (50 ml), extracted twice with ether (20 ml), the ether extract washed with water, and dried over magnesium sulphate. After removal of the ether the sample was analyzed by g.l.c.

In the second method, the hydrocarbon (0.5 gm) was dissolved in acetic acid (1 ml), and a mixture of nitric acid (0.1 ml), acetic anhydride (0.5 ml) and acetic acid (1 ml) run in dropwise with stirring and cooling. After 1½ hours the reaction was worked up as in the first method.

(b) Preparative scale runs. Both methods in (a) leave a large amount of the original hydrocarbon unreacted. Consequently, for preparative scale reactions more nitric acid was used, usually in the ratio of two moles nitric acid to 1 mole aromatic. These proportions use almost all the reactant hydrocarbon, but some disubstitution occurs, rendering the procedure unsuitable for analytical runs.

(c) Reactions for isolation of intermediates. The method of work-up was varied for reactions run to isolate the diene intermediates which decomposed to varying extents when the reaction was quenched and extracted in the normal way. The nitration was carried out as usual, in acetic anhydride solution, but quenched (for a run involving 5 gms of aromatic starting material) in 200 ml CCl_4. The CCl_4 was washed with water (3 x 100 ml) and dried with $MgSO_4$, and the CCl_4 removed under vacuum at, or only slightly above, room temperature. The dienes were isolated as described below. An alternative method of work-up involved removal of the solvent under vacuum at room temperature. This was, however, a lengthy procedure (8-12 hours).

These general procedures were occasionally modified, largely because of solubility problems with certain reactants. These modifications are noted for individual cases below.

Isolation of Final Products

(1) Mesitylene. When the reaction mixture was quenched with water, 2-nitromesitylene crystallized out, and was recrystallized from ethanol. It had m.p. 44° (lit.[55] 44°); N.m.r. ($CDCl_3$) δ = 2.27 (Ar-$C\underline{H}_3$, 6 protons), 2.31 (Ar-$C\underline{H}_3$, 3 protons) and 6.92 ppm (Ar-$\underline{H}$, 2 protons); I.R. (nujol) 1525, 1365 cm^{-1}. No further compounds were

found on extraction of the aqueous solution with ether.

(2) Pentamethyl benzene. The reaction mixture, worked up as described, was chromatographed on 5% deactivated alumina. Elution with light petroleum gave nitropentamethylbenzene, m.p. (recrystallized from ethanol) 62° (lit.[55] 63°); N.m.r. ($CDCl_3$) δ = 2.13 (Ar-C$\underline{H}_3$, 6 protons), 2.22 ppm (Ar-C$\underline{H}_3$, 9 protons); I.R. (CCl_4) 1520, 1370 cm^{-1}; mass spectrum, peaks at 193 (parent), 176 (M-OH), 163 (M-NO). Elution with benzene-light petroleum (1:9) gave 2,3,4,5-tetramethylbenzaldehyde as a yellow oil; N.m.r. ($CDCl_3$) δ = 2.03 (Ar-C$\underline{H}_3$, 6 protons), 2.10 (Ar-C$\underline{H}_3$, 3 protons), 2.50 (Ar-C$\underline{H}_3$, 3 protons), 7.36 (Ar-$\underline{H}$, 1 proton), 10.13 ppm (Ar-C$\underline{H}$O, 1 proton). The position of the formyl proton at 10.13 ppm fixes this as 2,3,4,5-tetramethylbenzaldehyde with only one methyl group ortho to the aldehyde[56]. I.R. (CCl_4) 1690 cm^{-1}; semicarbazone m.p. 219-20° (lit.[57] 221-2°; c.f. 2,3,4,6- and 2,3,5,6-tetramethylbenzaldehyde semicarbazones at 183-5° and 268-70° respectively[58]. Elution with benzene-light petroleum (1:1) gave 2,3,4,5-tetramethylphenylnitromethane; m.p. (recrystallized from ether/pentane) 51-2°; N.m.r. ($CDCl_3$) δ = 2.16 (Ar-C$\underline{H}_3$, 6 protons), 2.22 (Ar-C$\underline{H}_3$, 6 protons), 5.35 (Ar-C$\underline{H}_2NO_2$, 2 protons), 6.95 ppm (Ar-$\underline{H}$, 1 proton); I.R. (CCl_4) 1540, 1360 cm^{-1}; mass spectrum, peaks at 193 (parent), 164 (M-CHO), 147 (M-NO_2). The compound was fixed as

2,3,4,5-tetramethylphenylnitromethane by oxidation[59] with $KMnO_4$ to 2,3,4,5-tetramethylbenzaldehyde, identical with that already obtained directly from the reaction mixture.

(3) Hexamethylbenzene. This substrate is not very soluble in acetic acid or acetic anhydride, and therefore required a large amount of solvent. Hexamethylbenzene (1 gm) was dissolved in acetic acid (50 ml), and a solution of nitric acid (0.2 ml) and acetic anhydride (2 ml) in acetic acid (5 ml) was run in with stirring and cooling. The reaction was worked up after 1½ hours in the usual way, by quenching in water and extracting with ether. The mixture was then chromatographed on 5% deactivated alumina. Elution with light petroleum gave 2,3,4,5,6-pentamethylbenzyl acetate, m.p. (recrystallized from ether/pentane) 83-84° (lit.[54] 83-85°); N.m.r. ($CDCl_3$) δ = 2.05 (CO_2-C$\underline{H}_3$, 3 protons), 2.23 (Ar-C$\underline{H}_3$, 9 protons), 2.29 (Ar-C$\underline{H}_3$, 6 protons), 5.25 ppm (C$\underline{H}_2$-OAc, 2 protons); I.R. (CCl_4), 1740, 1230 cm^{-1}; mass spectrum, peaks at 220 (parent), 175 (M-C_2H_5O), 161 (M-OAc), 160 (M-HOAc). Elution with benzene gave 2,3,4,5,6-pentamethylphenylnitromethane, m.p. (recrystallized from ether/pentane) 78-80°; N.m.r. ($CDCl_3$) δ = 2.25 (Ar-C$\underline{H}_3$, 9 protons), 2.29 (Ar-C$\underline{H}_3$, 6 protons), 5.65 (C$\underline{H}_2$-NO_2, 2 protons); I.R. (CCl_4) 1540, 1360 cm^{-1}; mass spectrum, peaks at 207 (parent), 178 (M-CHO), 161 (M-NO_2).

(4) Prehnitene. The reaction mixture was chromatographed on 5% deactivated alumina. Elution with light petroleum gave a mixture of 5-nitroprehnitene and 5-acetoxyprehnitene. Elution with benzene-light petroleum (1:1) gave 2,3,4-trimethyphenylnitromethane as a yellow oil, which, after rechromatographing on 5% deactivated alumina was pure by g.l.c. N.m.r. (CCl_4) δ = 2.19, 2.24, 2.27 (Ar-C$\underline{H}_3$, 3 protons each), 5.33 (C$\underline{H}_2$-NO_2, 2 protons), 6.99 ppm (Ar-$\underline{H}$, 1 proton); I.R. (smear) 1545, 1365 cm^{-1}; mass spectrum, peaks at 150 (M-CHO), 133 (M-NO_2). Elution with benzene-ether (19:1) gave 5-acetoxy-6-nitroprehnitene. It had m.p. (recrystallized from ethanol) 81-2°; N.m.r. ($CDCl_3$), δ = 1.84 (CO_2-C$\underline{H}_3$, 3 protons), 1.92 (Ar-C$\underline{H}_3$, 9 protons), 1.95 ppm (Ar-C$\underline{H}_3$, 3 protons); I.R. (CCl_4), 1740, 1520, 1340, 1260 cm^{-1}; mass spectrum, peaks at 237 (parent; $C_{12}H_{15}NO_4$ requires 237.10010, found 237.10011), 220 (M-OH), 195 (M-CH_2CO), 178 (M-OAc), 177 (M-HOAc).

The mixture of 5-nitro- and 5-acetoxyprehnitene was refluxed for 2 hours with 5% sulphuric acid/methanol. The resultant mixture of 5-nitroprehnitene and 2,3,4,5-tetramethyl phenol was chromatographed on silica gel. Elution with light petroleum gave 5-nitroprehnitene, m.p. (recrystallized from ether pentane) 61° (lit.[55] 61°); N.m.r. ($CDCl_3$) δ = 2.24 (Ar-C$\underline{H}_3$, 6 protons), 2.29 (Ar-C$\underline{H}_3$, 3

protons), 2.83 (Ar-C$\underline{H}_3$, 3 protons), 7.40 ppm (Ar-$\underline{H}$, 1 proton); I.R. (CCl_4) 1510, 1360 cm^{-1}, mass spectrum, peaks at 179 (parent), 162 (M-OH). Elution with benzene gave 2, 3,4,5-tetramethylphenol, N.m.r. ($CDCl_3$) δ = 2.23 (Ar-C$\underline{H}_3$, 6 protons), 2.28 (Ar-C$\underline{H}_3$, 3 protons), 2.33 (Ar-C$\underline{H}_3$, 3 protons), 4.40 (-O$\underline{H}$, 1 proton, disappears on addition of D_2O), 6.99 ppm (Ar-$\underline{H}$, 1 proton). This was reacetylated by treatment with acetic anhydride in aqueous solution[53], to give 2,3,4,5-tetramethylphenyl acetate; m.p. (recrystallized from pentane) 56° (lit.[55] 56-57°); N.m.r. ($CDCl_3$) δ = 2.04 (CO_2-CH_3, 3 protons), 2.22 (Ar-C$\underline{H}_3$, 6 protons), 2.27 (Ar-C$\underline{H}_3$, 6 protons), 7.01 ppm (Ar-$\underline{H}$, 1 proton); I.R. (CCl_4) 1735, 1225 cm^{-1}; mass spectrum, peaks at 192 (parent), 150 (M-CH_2CO), 133 (M-OAc), 132 (M-HOAc). The material isolated after hydrolysis and reacetylation had g.l.c. retention time identical with the acetate in the mixture of nitro- and acetoxy- prehnitenes originally obtained.

2,3,4-trimethylphenylnitromethane was identified by $KMnO_4$ oxidation[59] to 2,3,4-trimethylbenzaldehyde, a yellow oil which had N.m.r. ($CDCl_3$) δ = 2.12, 2.23, 2.48 (Ar-C$\underline{H}_3$, 3 protons each), 7.03, 7.47 (doublets, J = 8 Hz, Ar-$\underline{H}$, 1 proton each), 10.13 ppm (-C$\underline{H}$O, 1 proton); I.R. (smear) 1700 cm^{-1}. The position of the formyl proton in the N.m.r. spectrum is consistent only with 2,3,4-trimethylbenzaldehyde, which has only one methyl group ortho to the aldehyde[56]. This was confirmed by the semicarbazone, m.p. 238° (lit.[60] 240-2°; c.f. 2, 3,6-trimethylbenzaldehyde semicarbazone m.p. 166-9° [58]).

(5) Durene. This substrate is extremely insoluble in acetic acid and acetic anhydride and reactions were initially run in acetonitrile solvent. To a solution of durene (1 gm) in acetonitrile (20 ml) was added a solution of nitric acid (0.2 ml) and acetic anhydride (2 ml) in acetonitrile (5 ml), with stirring and cooling in an ice-water bath. After 1½ hours the reaction was quenched with water (200 ml), extracted with ether (2 x 250 ml), the ether washed with water and dried ($MgSO_4$), and the ether removed. The mixture was then chromatographed on 5% deactivated alumina. Elution with light petroleum gave 3-nitrodurene; m.p. (recrystallized from pentane) 112° (lit.[55] 112-13°); N.m.r. (CCl_4) δ = 2.11, 2.25 (Ar-C$\underline{H}_3$, 6 protons each), 6.97 ppm (Ar-$\underline{H}$, 1 proton); I.R. (nujol) 1520, 1355 cm^{-1}. Elution with benzene-light petroleum (1:1) gave 2,4,5-trimethylbenzyl alcohol; m.p. (recrystallized from benzene) 82-3° (lit.[61] 83-3.5°); N.m.r. (CCl_4) δ = 2.22 (Ar-C$\underline{H}_3$, 6 protons), 2.28 (Ar-C$\underline{H}_3$, 3 protons), 4.51 (-$CH_2O\underline{H}$, 1 proton, disappears on addition of D_2O), 4.60 (-C$\underline{H}_2$OH, 2 protons), 6.95 (Ar-$\underline{H}$, 1 proton), 7.09 ppm (Ar-$\underline{H}$, 1 proton); I.R. 3300 cm^{-1} (broad); mass spectrum, peaks at 150 (parent, shifts to 151 on shaking with D_2O), 135 (M-CH_3), 132 (M-H_2O). Elution with benzene gave a mixture of 2,4,5-trimethylbenzaldehyde and 2,4,5-trimethylphenylnitromethane. These were separated by preparative T.L.C. on a silica plate,

developing with 5% acetone/chloroform and visualizing with u.v. light. The top band was 2,4,5-trimethylbenzaldehyde, a yellow oil which was T.L.C. pure; N.m.r. (CCl_4) δ = 2.28 (Ar-C$\underline{H}_3$, 6 protons), 2.50 (Ar-C$\underline{H}_3$, 3 protons), 7.00 (Ar-$\underline{H}$, 1 proton), 7.68 (Ar-$\underline{H}$, 1 proton), 10.14 ppm (-C$\underline{H}$O, 1 proton); I.R. 1700 cm^{-1}, mass spectrum, peaks at 148 (parent), 147 (M-H), 133 (M-CH_3), 119 (M-CHO). The second band was 2,4,5-trimethylphenylnitromethane; m.p. (recrystallized from ether/pentane) 50-51° (lit.[55] 52.5°); N.m.r. (CCl_4) δ = 2.20 (Ar-C$\underline{H}_3$, 6 protons), 2.28 (Ar-C$\underline{H}_3$, 3 protons), 5.26 (C$\underline{H}_2$-NO_2, 2 protons), 6.93 (Ar-$\underline{H}$, 1 proton), 7.01 ppm (Ar-$\underline{H}$, 1 proton); I.R. (nujol) 1545, 1365 cm^{-1}; mass spectrum, peaks at 179 (parent), 150 (M-CHO), 133 (M-NO_2).

Nitration was later carried out in acetic acid. Durene (1 gm) was dissolved in acetic acid (70 ml), and a solution of nitric acid (0.2 ml) and acetic anhydride (2 ml) in acetic acid (5 ml) was run in with stirring and cooling. The reaction was worked up as described for reaction in acetonitrile solution. The same products were shown by g.l.c. as were found for acetonitrile solution, but 3-acetoxydurene was also present. This was collected by preparative g.l.c. on a 6 ft x $\frac{1}{4}$" 6% FFAP on Chromosorb G column; N.m.r. (CCl_4) δ = 2.03 (CO_2-C$\underline{H}_3$, 3 protons), 2.24, 2.27, (Ar-C$\underline{H}_3$, 6 protons each), 7.03 ppm (Ar-$\underline{H}$, 1

proton); I.R. (CCl_4) 1765, 1220 cm^{-1}; mass spectrum, peaks at 192 (parent, $C_{12}H_{16}O_2$ requires 192.1150, found 192.1156), 150 ($M-CH_2CO$), 135 ($150-CH_3$).

(6) Isodurene. The reaction mixture was chromatographed on activated alumina. Elution with benzene-light petroleum (1:19) gave 4-nitroisodurene; m.p. (recrystallized from ether/pentane at dry ice/acetone temperatures) 40-41° (lit.[62] 39°); Nm.r. (CCl_4) δ = 2.10 (Ar-$C\underline{H}_3$, 3 protons), 2.15 (Ar-$C\underline{H}_3$, 6 protons), 2.23 (Ar-$C\underline{H}_3$, 3 protons), 6.83 ppm (Ar-$\underline{H}$, 1 proton); I.R. 1520, 1365 cm^{-1}; mass spectrum, peaks at 179 (parent, $C_{10}H_{13}NO_2$ requires 179.0946, found 179.0949), 162 (M-OH), 133 ($M-NO_2$). Elution with benzene-light petroleum (1:9) gave 4-acetoxyisodurene; m.p. (recrystallized from ether/pentane at dry ice/acetone temperatures) 41° (lit.[63] 40-41°); N.m.r. (CCl_4) δ = 2.03 ($CO_2-C\underline{H}_3$, 3 protons), 2.17 (Ar-$C\underline{H}_3$, 12 protons), 6.55 ppm (Ar-$\underline{H}$, 1 proton); I.R. (CCl_4) 1770, 1220 cm^{-1}; mass spectrum, peaks at 192 (parent, found 192.1147, $C_{12}H_{16}O_2$ requires 192.1150), 150 ($M-CH_2CO$), 135 ($150-CH_3$). Elution with ether-benzene (1:5) gave a mixture of 3,4,5-trimethylbenzaldehyde and 3,4,5-trimethylphenylnitromethane. These were separated by preparative T.L.C. on a silica plate, developing with 5% acetone/chloroform and visualizing with u.v. light. The top band was 3,4,5-trimethylbenzaldehyde, a yellow oil which was pure by T.L.C.; N.m.r. ($CDCl_3$) δ = 2.24

(Ar-C$\underline{H}_3$, 3 protons), 2.35 (Ar-C$\underline{H}_3$, 6 protons, 7.64 (Ar-$\underline{H}$, 2 protons), 9.93 ppm (-C$\underline{H}$O, 1 proton); I.R. (smear) 1695 cm^{-1}; mass spectrum, peaks at 148 (parent, $C_{10}H_{12}O$ requires 148.0888, found 148.0886), 147 (M-H), 119 (M-CHO). The position of the formyl proton in the N.m.r. spectrum fixes the compound as 3,4,5-trimethylbenzaldehyde[56]. The second band was 3,4,5-trimethylphenylnitromethane, a yellow oil pure by T.L.C.; N.m.r. (CCl_4) δ = 2.14 (Ar-C$\underline{H}_3$, 3 protons), 2.25 (Ar-C$\underline{H}_3$, 6 protons), 5.08 (C$\underline{H}_2$-NO_2, 2 protons), 6.99 ppm (Ar-$\underline{H}$, 2 protons); I.R. (smear) 1545, 1365 cm^{-1}; mass spectrum, peaks at 179 (parent, $C_{10}H_{13}NO_2$ requires 179.0946, found 179.0947) 163 (M-O), 150 (M-CHO), 133 (M-NO_2). Oxidation[59] ($KMnO_4$) gave 3,4,5-trimethylbenzaldehyde, identical with the aldehyde obtained directly from the nitration reaction.

(7) Pseudocumene. The reaction mixture was chromatographed on 10% deactivated alumina. Elution with light petroleum brought through a mixture of 3-, 5-, and 6-nitropseudocumenes, together with a small amount of either 3- or 5-acetoxypseudocumene. These were identified by comparison of g.l.c. retention times on FFAP and PDEAS columns with authentic samples of each compound. Elution with benzene-light petroleum (1:9) brought through an impure fraction which was rechromatographed on 5% deactivated alumina to give, on elution with benzene-light petroleum (1:1), pure 3,4-dimethylphenylnitromethane as a yellow oil; N.m.r. (CCl_4) δ = 2.23 (Ar-C$\underline{H}_3$, 6 protons), 5.23 (-C$\underline{H}_2NO_2$, 2 protons), 7.14 ppm (Ar-$\underline{H}$, 3 protons); I.R. (smear) 1550, 1375 cm^{-1}; mass spectrum, peaks at 149 (M-O), 119 (M-NO_2). Oxidation[59] with $KMnO_4$ gave

3,4-dimethylbenzaldehyde; N.m.r. ($CDCl_3$) δ = 2.30 (Ar-C<u>H</u>$_3$, 6 protons), 7.26 (Ar-<u>H</u>, doublet, 1 proton, J = 8 Hz), 7.60 (Ar-<u>H</u>, doublet, 1 proton, J = 8 Hz), 9.94 (-C<u>H</u>O, 1 proton); I.R. (smear) 1695 cm^{-1}. The position of the formyl proton establishes the compound as the 3,4- isomer, with no methyl groups ortho to the aldehyde[56]. The 2,4-dinitrophenylhydrazone had m.p. 229-30° (lit.[64] 231°; c.f. 221-2° and 214-5° respectively for the 2,4-dinitrophenylhydrazone derivatives of 2,4- and 2,5-dimethylbenzaldehydes[64]).

(8) <u>3-Bromo-o-xylene</u>. The reaction mixture showed three major compounds by g.l.c. These were collected by preparative g.l.c. on a 6 ft x $\frac{1}{4}$" 6% FFAP on Chromosorb G column. In order of appearance from the column, these were (a) 6-Nitro-3-bromo-<u>o</u>-xylene; N.m.r. (CCl_4) δ = 2.40, 2.45 (Ar-C<u>H</u>$_3$, 3 protons each), 7.39, 7.44 ppm (Ar-<u>H</u>, 1 proton each); mass spectrum, peaks at 229 (parent; found 228.9737, $C_8H_8NO_2$ Br requires 228.9739), 212 (M-OH). The predominant loss of OH in the mass spectrum fixes this as 6-nitro-3-bromo-<u>o</u>-xylene, the isomer with the nitro group ortho to a methyl group[65]. (b) 4-Nitro-3-bromo-<u>o</u>-xylene. N.m.r. (CCl_4) δ = 2.40, 2.42 (Ar-C<u>H</u>$_3$, 3 protons each), 7.11, 7.36 ppm (Ar-<u>H</u>, 1 proton each, doublets J = 8 Hz); mass spectrum, peaks at 229 (parent, found 228.9742), 199 (M-NO), 183 (M-NO_2). The 8 Hz coupling indicates ortho ring protons[66] and the mass spectrum shows that the nitro group is not ortho to a methyl group. The compound is therefore the 4-nitro-3-bromo- isomer. (c) 5-Nitro-3-bromo-<u>o</u>-xylene; N.m.r. δ = 2.40, 2.45 (Ar-C<u>H</u>$_3$, 3 protons each), 7.43, 7.56 ppm

(Ar-H, 1 proton each); mass spectrum, peaks at 229 (parent, found 228.29739, $C_8H_8NO_2Br$ requires 228.9739), 199 (M-NO), 183 ($M-NO_2$). 5-Acetoxy-3-bromo-o-xylene was present in 1-2% yield. It had mass spectrum 242 (parent, found 241.9941, $C_{10}H_{11}O_2Br$ requires 241.9943), 200 ($M-CH_2CO$), 185 ($200-CH_3$), and its g.l.c. retention time was identical with that of the material formed on decomposition of 1-nitro-6-bromo-4-acetoxy-1,2-dimethylcyclohexa-2,5-diene (see p.52).

(9) 4-Bromo-o-xylene. The reaction mixture showed four major compounds by g.l.c. and these were collected by preparative g.l.c. on a 6ft x $\frac{1}{4}$" 6% FFAP on Chromosorb G column. In order of appearance from the column, these were (a) 6-Nitro-3, 4-xylenol; N.m.r. (CCl_4) δ = 2.23 (Ar-CH_3, 3 protons), 2.29 (Ar-CH_3, 3 protons), 6.85 (Ar-H, 1 proton), 7.75 (Ar-H, 1 proton), 10.28 (-OH, 1 proton); I.R. (CCl_4) 3260, 1615, 1320 cm^{-1}; mass spectrum, peaks at 167 (parent, found 167.0587, $C_{10}H_9NO_3$ requires 167.0582), 152 ($M-CH_3$), 150 (M-OH), 137 (M-NO). The ortho-nitrophenol structure with intramolecular hydrogen bonding is established by the N.m.r.[67] and I.R.[68] hydroxyl peak positions; the N.m.r. establishes[66] para aromatic protons (J = 0). This compound was identical with 6-nitro-3,4-xylenol synthesized by nitration of 3,4-xylenol with nitric acid in acetic acid solution[69]. (b) 3-Nitro-4-bromo-o-xylene; N.m.r. ($CDCl_3$)

δ = 2.32, 2.35 (Ar-C$\underline{H}_3$, 3 protons each), 7.20, 7.59 ppm (Ar-$\underline{H}$, 1 proton each, doublets, J = 8 Hz); mass spectrum, peaks at 229 (parent, found 228.9441, $C_8H_8NO_2Br$ requires 228.9739), 212 (M-OH). The N.m.r. establishes[66] the ortho aromatic protons (J = 8 Hz). (c) 6-Nitro-4-bromo-o-xylene; N.m.r. ($CDCl_3$) δ = 2.30, 2.38 (Ar-C$\underline{H}_3$, 3 protons each), 7.12, 7.34 ppm (Ar-$\underline{H}$, 1 proton each); mass spectrum, peaks at 229 (parent, found 228.9436), 212 (M-OH). Major loss of OH in the mass spectrum confirms that the nitro group is ortho to a methyl[65]. (d) 5-Nitro-4-bromo-o-xylene; N.m.r. ($CDCl_3$) δ = 2.32 (Ar-C$\underline{H}_3$, 6 protons), 7.51, 7.70 ppm (Ar-$\underline{H}$, 1 proton each); mass spectrum, peaks at 229 (parent, found 228.9734), 199 (M-NO), 183 ($M-NO_2$). The mass spectrum shows loss of NO and NO_2, but no loss of OH, the expected pattern for this isomer.

(10) 4-Acetoxy-o-xylene. Analysis of the reaction mixture by g.l.c. showed three compounds, and these were collected by preparative g.l.c. on a 4 ft x $\frac{1}{4}$" 10% SE-30 on Chromosorb G column. In order of appearance from the column these were (a) 6-Nitro-3,4-xylenol, identical to that collected from the nitration of 4-bromo-o-xylene and of 3,4-xylenol. (b) 6-Nitro-3,4-xylenyl acetate; N.m.r. ($CDCl_3$) δ = 2.33 (Ar-C$\underline{H}_3$, $CO_2C\underline{H}_3$, 9 protons), 7.00 (Ar-$\underline{H}$, 1 proton), 7.92 ppm (Ar-$\underline{H}$, 1 proton); I.R. (CCl_4), 1800, 1540, 1360, 1200 cm^{-1}; mass spectrum, peaks at 209 (parent), 167

($M-CH_2CO$), 152 ($167-CH_3$), 150 ($167-OH$), 137 ($167-NO_2$), 121 ($167-NO_2$). This substance was identical to that prepared from 6-nitro-3,4-xylenol by refluxing with acetic anhydride. (c) 2-Nitro- or 5-nitro-3,4-xylenyl acetate; mass spectrum, peaks at 209 (parent), 167 ($M-CH_2CO$), 152 ($167-CH_3$), 150 ($167-OH$), 137 ($167-NO$), 121 ($167-NO_2$).

(11) p-Xylene. The reaction mixture contained three products which were collected by preparative g.l.c. on a 4 ft x $\frac{1}{4}$" 10% FFAP on Chromosorb G column. In order of appearance from the column these were (a) 2-Acetoxy-p-xylene; N.m.r. ($CDCl_3$) δ = 2.13 ($CO_2-C\underline{H}_3$, 3 protons), 2.26 ($Ar-C\underline{H}_3$, 6 protons), 6.84 (Ar-H, 1 proton), 6.94, 7.13 ppm (Ar-H, doublets, J = 8 Hz, 1 proton each); I.R. (smear) 1760, 1220 cm^{-1}. This material was identical to an authentic sample prepared from 2,5-xylenol and acetic anhydride[53]. (b) p-Methylbenzyl acetate; N.m.r. (CCl_4) δ = 2.03 ($CO_2-C\underline{H}_3$, 3 protons), 2.33 ($Ar-C\underline{H}_3$, 3 protons), 6.66 ($C\underline{H}_2-OAc$, 2 protons), 7.15 (Ar-H, 4 protons); I.R. (smear) 1740, 1230 cm^{-1}. The compound was identical to an authentic sample prepared from oxidation of p-xylene with lead tetraacetate[70]. (c) 2-Nitro-p-xylene; N.m.r. ($CDCl_3$) δ = 2.38, 2.54 ($Ar-C\underline{H}_3$, each 3 protons), 7.25 (Ar-H, 2 protons); 7.77 (Ar-H, 1 proton); I.R. (smear) 1515, 1360 cm^{-1}. The compound was identical to an authentic sample prepared from p-xylene and nitric acid[71].

(12) 3- and 4-Deutero-o-xylenes. The reaction mixture was subjected to preparative g.l.c. on a 6 ft x ¼" 6% FFAP on Chromosorb G column. The three components were collected, their identity checked by comparison of retention times with authentic samples, and analyzed by mass spectrometry for deuterium content.

Isolation of Diene Intermediates

In this section, the more stable of a pair of isomeric dienes will be designated isomer A, and the less stable, isomer B.

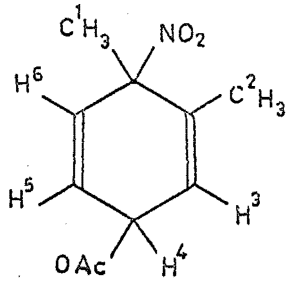
(1) o-Xylene. The reaction mixture, which had been worked up as described, was chromatographed on 10% deactivated alumina. Elution with light petroleum brought through the aromatics, and elution with light petroleum-ether (49:1) brought through a mixture of cis and trans isomers of 1-nitro-4-acetoxy-1,2-dimethylcyclohexa-2,5-diene. This mixture was adsorbed onto 5% deactivated alumina, left for an hour to allow the less stable isomer to decompose, and then chromatographed. Light petroleum eluted the aromatic acetate; ether-light petroleum (1:19) eluted diene isomer A as a yellow oil which could be crystallized out of pentane at dry ice-acetone temperatures. It had m.p. 25-30°; N.m.r. (CCl_4) δ = 1.70 (s, C^1H_3, 3 protons), 1.78[t,J(C^2H_3,H^3) 1.0

Hz, J(C^2H_3,H^4) 1.5 Hz C^2H_3, 3 protons], 2.04 (s, OAc, 3 protons), 5.54 [m, J(H^4,C^2H_3) 1.5 Hz, J(H^4,H^3) 2.0 Hz, J(H^4, H^5) 2.0 Hz, H^4, 1 proton], 5.85 [m,J(H^3,C^2H_3) 1.0 Hz, J(H^3,H^4) 2.0 Hz, H^3, 1 proton], 6.01[d,J(H^5, H^4) 2.0 Hz, H^5, 1 proton], 6.01 ppm (s, H^6, 1 proton); I.R. (smear) 1735, 1540, 1370, 1225 cm^{-1}; u.v. (cyclohexane) λ_{max} = 204 nm, ε_{max} = 8400.

When the mixture of dienes was rechromatographed on 10% deactivated alumina, continued elution with light petroleum gave a small amount of isomer B in the twelfth fraction, also as a yellow oil. N.m.r. (CCl_4) δ = 1.78 (s, C^1H_3, 3 protons), 1.84[t, J(C^2H_3, H^3) 1.0 Hz, J (C^2H_3, H^4) 1.0 Hz, C^2H_3, 3 protons], 2.03 (s, OAc, 3 protons), 5.72 [m, J(H^4, C^2H_3) 1.0 Hz, J(H^4, H^3) 2.5 Hz, J(H^4, H^5) 2.5 Hz, H^4, 1 proton], 5.86 [m, J(H^3, C^2H_3) 1.0 Hz, J(H^3, H^4) 2.5 Hz, H^3, 1 proton], 6.03 [d, J(H^5, H^4) 2.0 Hz, H^5, 1 proton], 6.03 ppm [s, H^6, 1 proton]; I.R. (smear) 1730, 1540, 1365, 1215 cm^{-1}; u.v. (cyclohexane) λ_{max} = 208.5 nm, ε_{max} = 12,600.

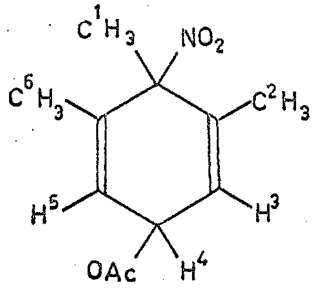
About 25-30% of the original quantity of dienes decomposes into 4-acetoxy-o-xylene during chromatography on 10% deactivated alumina, and nearly all isomer B, and about half isomer A, decomposes during chromatography on 5% deactivated alumina. The dienes were therefore always con-

taminated with aromatic acetate, but samples better than 95% pure were obtained in each case.



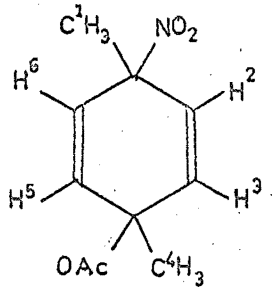
(2) Hemimellitene. The reaction mixture, worked up as described, was chromatographed on 10% deactivated alumina. Light petroleum eluted the aromatic material and ether-light petroleum (1:49) eluted a mixture of cis and trans isomers of 1-nitro-4-acetoxy-1,2,6-trimethylcyclohexa-2,5-diene. This mixture was crystallized from ether/pentane. The first crop of crystals consisted of pure isomer A; m.p. 60° (decomp.); N.m.r. (CCl_4) δ = 1.68 (s, C^1H_3 3 protons), 1.76[t, J(C^6H_3 and C^2H_3, H^5 and H^3) 0.5 Hz, J(C^6H_3 and C^2H_3, H^4) 1.5 Hz, C^6H_3, C^2H_3, 6 protons], 2.06 (s, OAc, 3 protons), 5.53[m, J(H^4, C^6H_3 and C^2H_3) 1.5 Hz, J(H^4, H^3 and H^5) 2.5 Hz, H^4, 1 proton] 5.79 ppm [m, J(H^3 and H^5, C^6H_3 and C^2H_3) 0.5 Hz, J(H^3 and H^5, H^4) 2.5 Hz, H^3 and H^5, 2 protons]; I.R. (nujol) 1740, 1540, 1370, 1225 cm^{-1}; u.v. (cyclohexane) λ_{max} = 204.5 nm, ε_{max} = 7,300.

The second crop of crystals was a mixture of two diene isomers; the third crop was pure isomer B. N.m.r. (CCl_4) δ = 1.77 (s, C^1H_3, 3 protons), 1.79 [t, J(C^6H_3 and C^2H_3, H^4) 1.0 Hz, J(C^6H_3 and C^2H_3, H^3 and H^5) 0.5 Hz, C^6H_3 and C^2H_3, 6 protons], 2.01 (s, oAc, 3 protons) 5.65 [m, J(H^4, C^6H_3 and C^2H_3) 1.0 Hz, J (H^4, H^3 and H^5) 4.0 Hz, H^4, 1 proton], 5.82 ppm [m, J(H^3 and H^5, C^6H_3 and C^2H_3) 0.5 Hz, J(H^3 and H^5, H^4) 4.0 Hz, H^3 and H^5, 2 protons]; I.R. (nujol) 1730, 1540, 1375, 1225 cm^{-1}; u.v. (cyclohexane) λ_{max} = 203.5 nm, ε_{max} = 11,200.



(3) p-Xylene. The reaction mixture after work-up was chromatographed on 10% deactivated alumina. Elution with light petroleum gave the aromatic products. Elution with ether-light petroleum (1:49) gave one of the isomers of 1-nitro-4-acetoxy-1,4-dimethylcyclohexa-2,5-diene (isomer B) as a yellow oil. N.m.r. (CCl_4) δ = 1.45 (s, C^4H_3, 3 protons), 1.76 (s, C^1H_3, 3 protons), 1.93 (s, oAc, 3 protons), 6.03

ppm (s, ring protons, 4 protons); I.R. (smear) 1740, 1545, 1365, 1240 cm^{-1}; u.v. (cyclohexane), λ_{max} = 196.5 nm, ε_{max} = 15,800. Further elution with ether-light petroleum (1:49) gave isomer A, also as a yellow oil; N.m.r. (CCl_4) δ = 1.53 (s, C^4H_3, 3 protons), 1.67 (s, C^1H_3, 3 protons), 1.94 (s, oAc, 3 protons), 6.21 ppm (s, ring protons, 4 protons); I.R. (smear) 1740, 1545, 1365, 1240 cm^{-1}; u.v. (cyclohexane) λ_{max} = 196.5 nm, ε_{max} = 16,900.

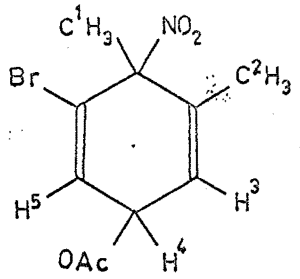


(4) 3-Bromo-o-xylene. The reaction mixture was chromatographed on 10% deactivated alumina. Elution with light petroleum brought through the aromatic products. Elution with benzene-light petroleum (1:19) brought through a mixture of the two isomers of 1-nitro-6-bromo-4-acetoxy-1,2-dimethylcyclohexa-2,5-diene. These were partially separated, the first few fractions containing about 75% of isomer A and 25% of isomer B, while the tail fractions contained about 75% isomer B and 25% isomer A. The fractions

rich in isomer A were combined and heated in acetic acid until the N.m.r. spectrum showed the complete decomposition of isomer B. Chromatography on 5% deactivated alumina then gave, on elution with ether-light petroleum (1:19), a pure sample of isomer A as a yellow oil. On recrystallization from pentane it had m.p. 75-78°. N.m.r. (CCl_4) δ = 1.80 [t, J(C^2H_3, H^3) 1.0 Hz, J(C^2H_3, H^4) 1.0 Hz, C^2H_3, 3 protons], 1.82 (s, C^1H_3, 3 protons), 2.08 (s, oAc, 3 protons), 5.56 [m, J(H^4, C^2H_3) 1.0 Hz, J(H^4, H^3) 3.5 Hz, J(H^4, H^5) 3.5 Hz, H^4, 1 proton], 5.80 [m, J(H^3, C^2H_3) 1.0 Hz, J(H^3, H^4) 3.5 Hz, J(H^3, H^5) 1.5 Hz, H^3, 1 proton], 6.50 ppm [q, J(H^5, H^4) 3.5 Hz, J(H^5, H^3) 1.5 Hz, H^5, 1 proton]; I.R. (smear) 1740, 1540, 1340, 1225 cm^{-1}; u.v. (cyclohexane) λ_{max} = 200 nm, ε_{max} = 11,700.

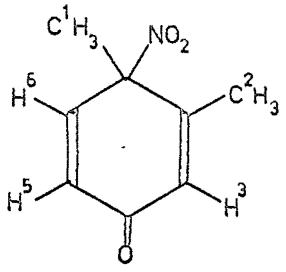
The fractions rich in the isomer B were rechromatographed on 5% deactivated alumina. Elution with benzene-light petroleum (1:9) gave mostly mixed isomers, but continued elution gave a small tail fraction of isomer B, also a yellow oil, in pure form. N.m.r. (CCl_4) δ = 1.82 [t, J(C^2H_3, H^3) 1.0 Hz, J(C^2H_3, H^4) 1.0 Hz, C^2H_3, 3 protons], 1.91 (s, C^1H_3, 3 protons), 2.03 (s, oAc, 3 protons), 5.76 [m, J(H^4, C^2H_3) 1.0 Hz, J(H^4, H^5) 4.0 Hz, H^4, 1 proton], 5.82 [m, J(H^3, C^2H_3) 1.0 Hz, J(H^3, H^5) 2.0 Hz, H^3, 1 proton], 6.50 ppm [q, J(H^5, H^4) 2.0 Hz, J(H^5, H^3) 4.0 Hz, H^5, 1

proton]; I.R. (smear) 1730, 1540, 1340, 1225 cm^{-1}; u.v. (cyclohexane) λ_{max} = 203.5 nm, ε_{max} = 13,300.



(5) 4-Bromo-o-xylene and 4-acetoxy-o-xylene. The reaction was worked up by removal of solvents at room temperature under vacuum, and the mixture chromatographed on 10% deactivated alumina. Elution with light petroleum brought through the aromatic products; elution with ether-light petroleum (1:19) gave 4-nitro-3,4-dimethylcyclohexa-2,5-dienone as white crystals after removal of the solvent. It had m.p. 76-77° (decomp.); N.m.r. ($CDCl_3$, 0°) δ = 1.92 (s, C^1H_3, 3 protons), 2.05 [d; $J(C^2H_3, H^3)$ 1.0 Hz, C^2H_3, 3 protons], 6.25 [m, $J(H^3, C^2H_3)$ 1.0 Hz, $J(H^3, H^5)$ 1.5 Hz, H^3, 1 proton], 6.40 [q, $J(H^5, H^3)$ 1.5 Hz, $J(H^5, H^6)$ 10.0 Hz, H^5, 1 proton], 6.90 [d, $J(H^6, H^5)$ 10.0 Hz, H^6, 1 proton], I.R. 1670, 1630, 1610, 1540, 1370 cm^{-1}; u.v. (cyclohexane) λ_{max} = 224 nm, ε_{max} = 10,000; mass spectrum, peaks at 167 (parent, found 167.0575, $C_8H_9NO_3$ requires

167.0582), 121 ($M-NO_2$).



This dienone decomposes in a few hours in solution at room temperature in most solvents, but is stable in the solid state in a desiccator for several days.

Decomposition of Diene Intermediates

(a) o-Xylene and hemimellitene. Samples of each of the diene isomers from these hydrocarbons were decomposed by heating in acetic acid or propionic acid. Each gave a 95% yield of the corresponding aromatic acetate (4-acetoxy-o-xylene or 5-acetoxyhemimellitene) identified by comparison with authentic samples. Injection of samples of both isomers of these dienes directly onto a g.l.c. column (FFAP at 150°) also produced the aromatic acetate as the only detectable product.

(b) 3-Bromo-o-xylene. Each of the diene isomers from this substrate were decomposed by heating in acetic acid. Each gave a 95% yield of 5-acetoxy-3-bromo-o-xylene,

isolated by chromatography on 10% deactivated alumina as a pale yellow oil. N.m.r. (CCl_4) δ = 2.14 (OAc, 3 protons), 2.26 (Ar-CH_3, 6 protons), 6.74, 7.09 (Ar-H doublets, J = 2.5 Hz, 1 proton each); I.R. (smear) 1770, 1210 cm^{-1}; mass spectrum, peaks at 242 (parent), 200 (M-CH_2CO), 185 (200-CH_3). The coupling between the aromatic protons establishes them as meta to each other[66]. Injection of samples of both isomers onto a g.l.c. column (FFAP at 150°) produced 3-bromo-o-xylene (96%) and 5-acetoxy-3-bromo-o-xylene (4%).

(c) p-Xylene. Both isomers of the diene decompose into more than one product. Samples of each of the isomers were heated in acetic acid containing a little nitromethane as a standard, and the proportions of the products formed determined by N.m.r. analysis of the mixtures before and after heating. Samples were also decomposed in propionic acid, and in a saturated solution of sodium propionate/propionic acid. In neither case was any evidence found of incorporation of propionate into the product. Samples of each of the isomers were injected onto a g.l.c. column (FFAP at 150°). The proportions of the products formed (p-xylene and 2-acetoxy-p-xylene) were determined by injecting a weighed amount of diene together with a weighed amount of nitrobenzene, after first calibrating the response of the instrument for each of the products, and for nitrobenzene.

(d) 4-Bromo-o-xylene. The dienone intermediate obtained from this substrate was decomposed in a number of solvents and the products analyzed by g.l.c. (FFAP and SE-30 columns). On dissolving the dienone (100 mgs) in acetic anhydride (1 ml), shaking the solution for several minutes with water (25 ml), and extracting with ether (this is the method of work-up usually employed for the nitration reaction), the product was 6-nitro-3,4-xylenol in 85% yield, with several minor products. However, decomposition of the dienone by overnight standing in various other solvents (acetic acid, chloroform, DMSO) produced in each case a mixture of 6-nitro-3,4-xylenol (65%) and 2-nitro-3,4-xylenol (35%); these decompositions were cleaner than those occurring on shaking with water, with virtually no other products. The two phenols were separated by chromatography on silica gel. Elution with benzene-light petroleum (2:3) gave 6-nitro-3,4-xylenol; elution with benzene-light petroleum (3:2) gave 2-nitro-3,4-xylenol. It had m.p. (recrystallized from pentane) 70-71° (lit.[69] 72°); N.m.r. (CCl_4) δ = 2.27 (Ar-C$\underline{H}_3$, 3 protons), 2.39 (Ar-C$\underline{H}_3$, 3 protons) 6.82, 7.22 (Ar-$\underline{H}$, doublets, J = 8.5 Hz, 1 proton each), 9.25 ppm (O$\underline{H}$, 1 proton); I.R. (CCl_4) 3300, 1530, 1330 cm^{-1}; mass spectrum, peaks at 167 (parent), 150 (M-OH), 137 (M-NO). When decomposition was carried out in acetic acid containing added sodium acetate or added sodium bromide,

the same products were obtained, with no incorporation of acetate or bromide into the product. When decomposition was carried out in acetic acid containing added 3,5-dimethylphenol the same products were again observed, with no nitration of the added phenol.

(e) Kinetics of decomposition. Competitive decompositions of the two diene isomers from o-xylene, hemimellitene, and 3-bromo-o-xylene were followed by N.m.r. The reactions were carried out at 20° or 40° by dissolving mixtures of the two isomers in acetic acid-d_4 (for 3-bromo-o-xylene) or 1:1 mixtures of acetic acid-d_4 and CCl_4 (for the other dienes, which decomposed too quickly in pure acetic acid-d_4). Under these conditions the dienes had half-lives of several hours, with the exception of those from 3-bromo-o-xylene which decomposed only over a period of weeks. The decomposition was followed by integrating the distinguishable peaks of each isomer (the methyl groups; also the ring protons in the dienes from p-xylene and 3-bromo-o-xylene), and using nitromethane as an internal standard. The ratio of the relative extents of decomposition of the two isomers was in each case extrapolated back to zero time to give the relative reactivities of the isomers.

N.m.r. Analyses of Crude Reaction Mixtures

A sample of the reaction mixture before work-up was taken, two drops of nitromethane added as an internal standard, and the N.m.r. spectrum and integral run. The sample was then heated at 60° until the intermediates had decomposed (about one hour), and the N.m.r. and integral rerun. It was shown that heating at 60° for an hour resulted in no loss of nitromethane by subjecting a solution of nitromethane (b.p. 100°) and maleic anhydride (b.p. 199° , and which therefore should not be lost as readily on heating) to heat at 60° for an hour in an N.m.r. tube; there was no difference in the relative integrals before and after heating.

Nitrations with Acetyl Nitrate

To a solution of aromatic hydrocarbon (0.5 ml) and dried silver nitrate (0.8 gm) in acetonitrile (5 ml) was added a solution of redistilled acetyl chloride (0.4 gm) in acetonitrile (1 ml), with stirring and cooling. After 1½ hours the reaction was quenched in water (100 ml), extracted twice with ether (25 ml) and the ether extracts washed with water and dried ($MgSO_4$).

Nitrations with HNO_3/H_2SO_4 in Acetic Acid

To a solution of o-xylene (0.5 ml) in acetic acid (3 ml) was added a solution of nitric acid (0.1 ml) and sulphuric acid (0.25 ml) in acetic acid (1 ml), with stirring and cooling. After 1½ hours the reaction was quenched with water (100 ml), extracted twice with CCl_4 (25 ml) and the extracts washed with water and dried ($MgSO_4$). It was shown by N.m.r. (by which acetic acid and acetic anhydride are clearly distinguishable) that sulphuric acid and acetic acid in these proportions do not form acetic anhydride even after several hours. Similarly, no acetic anhydride was detected in mixtures of acetic acid, nitric acid and sulphuric acid in these proportions.

Low Temperature Nitrations in Chloroform

A solution of o-xylene (0.5 ml), either alone or together with acetic acid or acetic anhydride (0.25 ml), in chloroform (5 mls) was cooled to -20°. A solution of nitric acid (0.1 ml) and acetic anhydride (0.25 ml) in chloroform (2 mls) was also cooled to -20°, and then added dropwise with stirring over half an hour, maintaining the temperature at -20°. After addition the reaction was quenched in water (100 ml) and extracted with chloroform. The extract, after drying and removal of solvent, was analyzed by g.l.c.

Kinetics of Nitration by Nitric Acid/Acetic Anhydride in Acetic Acid

(1) Nitration of Mesitylene and m-Xylene

(a) Method of analysis. The reactions were followed spectrophotometrically, measuring the rates of formation of the mono-nitrohydrocarbons. Nitromesitylene was measured at 337.5 nm (shoulder, $\varepsilon = 5.13 \times 10^2$), and the mixed 2- and 4-nitro-m-xylenes at 335 nm ($\varepsilon = 8.26 \times 10^2$ for 15% 2-nitro-m-xylene, and 85% 4-nitro-m-xylene, which are the proportions formed in the reaction). Nitric acid, acetic acid, acetic anhydride, mesitylene and m-xylene do not absorb above 300 nm. Calibration runs were done to ensure that solutions of nitromesitylene and 2- and 4-nitro-m-xylenes obey Beer's law over the range of concentrations which occur during the reactions.

(b) Procedure. Two solutions were made up, one consisting of a weighed amount of acetic acid and a weighed amount of hydrocarbon, and the other of weighed amounts of acetic acid, acetic anhydride and nitric acid. These solutions were brought to 30° in a water bath maintained at this temperature, and then mixed rapidly, and a sample of the mixture transferred to a 1 cm cell held at 30° in the sample compartment of the spectrometer. The reference cell contained a solution of nitric acid and acetic anhydride in acetic acid, made up to the concentrations of these substances in the reaction mixture. The change in absorption

with time of the reaction mixture was followed at the wavelengths given above. No dinitration occurred under these conditions, since no change in absorption over a period of several hours at the wavelengths used was observed on treating nitromesitylene and the nitro-m-xylenes with nitric acid/acetic anhydride under these conditions. No products other than the nitro-aromatics could be detected by g.l.c. in the mixtures after the reactions had been completed.

(2) Competitive Nitrations

(a) Procedure. A solution of weighed amounts of m-xylene and mesitylene (approx. 0.03 gm) in acetic acid (50 ml) was made up, and brought to 30° in a water bath maintained at this temperature. A mixture of a weighed amount of nitric acid (approx 0.7 gm), acetic anhydride (5 mls) and acetic acid (5 mls) was also brought to 30°, and the two solutions mixed rapidly, and maintained at 30°. Aliquots (10 mls) were withdrawn at various time intervals, quenched in water (100 mls), extracted twice with CCl_4 (50 ml), the extracts washed twice with water, and dried with $MgSO_4$. The CCl_4 was then removed and the samples analyzed, and the product ratios extrapolated back to zero time to give the relative reactivities of the aromatic substrates.

It was shown by subjecting weighed amounts of the nitro-aromatic products to this extraction procedure that all the nitrated material is recovered.

Several other pairs of aromatic hydrocarbons were also nitrated in this way - m-xylene/o-xylene, o-xylene/toluene and toluene/benzene. In the case of o-xylene/toluene, 20 ml aliquots were taken because of the lesser reactivity of these compounds, so that sufficient material was available for analysis. In the case of toluene/benzene, the whole reaction mixture was worked up after 45 minutes, and the product ratios found were used to give relative reactivities. The nitration of m-xylene followed by u.v. showed that after 45 minutes there was only about 10% reaction; toluene and benzene are much less reactive than m-xylene, so that after 45 minutes, reaction will have occurred only to the extent of 1-2%. Little error should therefore be introduced by taking relative reactivities directly from product ratios after this time.

(b) Method of analysis. The mixtures were analyzed by g.l.c. using an FFAP column, after calibrating the detector for its response to the various reaction products. This column completely separated the nitro-m-xylene isomers from nitromesitylene, and the nitrotoluene isomers from nitrobenzene, but did not achieve a complete separation of the products from m-xylene/o-xylene (4-nitro-m-xylene and

3-nitro-o-xylene came through together) or o-xylene/toluene (4-acetoxy-o-xylene and p-nitrotoluene came through together). In these cases the estimation of products was done using the peaks for those of the products which were completely separated, together with the isomer distributions found by Wright[7] (see P.109). These isomer distributions were checked by nitration of each of the compounds separately under the conditions used for the competitive nitrations.

RESULTS

Product distributions with nitric acid-acetic anhydride

The product ratios given here are those determined by g.l.c. analysis after work-up of the reaction mixture, and are all averages over a number of runs. Some figures are more reliable than others, since in some cases only a small amount of starting material was available, and only a few runs could be made.

(1) Nitration of mesitylene with nitric acid-acetic anhydride (3 runs)

2-nitromesitylene	100%

(2) Nitration of p-xylene with nitric acid-acetic anhydride (6 runs)

2-nitro-p-xylene	39 ± 3%
2-acetoxy-p-xylene	35 ± 3%
p-methylbenzyl acetate	26 ± 2%

(3) Nitration of isodurene with nitric acid-acetic anhydride (3 runs)

4-nitroisodurene	73 ± 3%
4-acetoxyisodurene	5 ± 2%
3,4,5-trimethylbenzaldehyde	7 ± 1%
3,4,5-trimethylphenyl-nitromethane	15 ± 2%

(4) Nitration of durene with nitric acid-acetic anhydride

	HOAc solution (6 runs)	Ac_2O solution (6 runs)	CH_3CN solution (6 runs)
2-nitrodurene	49 ± 3%	52 ± 3%	72 ± 4%
2-acetoxydurene	31 ± 2%	33 ± 2%	3 ± 1%
2,4,5-trimethylbenzyl alcohol	6 ± 1%	-	12 ± 2%
2,4,5-trimethylbenzaldehyde	3 ± 1%	3 ± 1%	7 ± 1%
2,4,5-trimethylphenyl-nitromethane	11 ± 2%	12 ± 2%	6 ± 1%

(5) Nitration of prehnitene with nitric acid-acetic anhydride (3 runs)

5-nitroprehnitene	25 ± 2%
5-acetoxyprehnitene	43 ± 3%
5-nitro-6-acetoxyprehnitene	11 ± 1%
2,3,4-trimethylphenylnitromethane	21 ± 2%

(6) Nitration of pentamethylbenzene with nitric acid-acetic anhydride (6 runs)

Nitropentamethylbenzene	55 ± 3%
2,3,4,5-tetramethylphenylnitromethane	37 ± 3%
2,3,4,5-tetramethylbenzaldehyde	8 ± 2%

(7) Nitration of hexamethylbenzene with nitric acid-acetic anhydride (6 runs)

Pentamethylbenzyl acetate	75 ± 3%
Pentamethylphenylnitromethane	25 ± 3%

(8) Nitration of pseudocumene with nitric acid-acetic anhydride (6 runs)

3-nitropseudocumene	10 ± 2%
5-nitropseudocumene	35 ± 3%
6-nitropseudocumene	4 ± 1%
3- and 5-acetoxypseudocumene	3 ± 1%
3,4-dimethylphenylnitromethane	41 ± 3%

(9) Nitration of 3-bromo-o-xylene with nitric acid-acetic anhydride (3 runs)

6-nitro-3-bromo-o-xylene	72 ± 3%
4-nitro-3-bromo-o-xylene	20 ± 2%
5-nitro-3-bromo-o-xylene	6 ± 1%
5-acetoxy-3-bromo-o-xylene	2 ± 1%

(10) Nitration of 4-bromo-o-xylene with nitric acid-acetic anhydride (6 runs)

5-nitro-4-bromo-o-xylene	42 ± 3%
6-nitro-3,4-xylenol	40 ± 3%
3-nitro-4-bromo-o-xylene	9 ± 2%
6-nitro-4-bromo-o-xylene	9 ± 2%

(11) Nitration of 4-acetoxy-o-xylene with nitric acid-acetic anhydride (3 runs)

6-nitro-3,4-xylenol	67 ± 3%
5-nitro-4-acetoxy-o-xylene	25 ± 2%
3- and 6-nitro-4-acetoxy-o-xylene	8 ± 2%

Table I

Nitrations of o-xylene in various media

Product	With preformed acetyl nitrate in acetonitrile	With HNO_3/Ac_2O in acetonitrile	With HNO_3/H_2SO_4 in acetic acid
4-acetoxy-o-xylene	39%	40%	45%
4-nitro-o-xylene	39%	36%	36%
3-nitro-o-xylene	22%	24%	20%

Table II

Dependence of products from durene on nitrous acid concentration - ratios on nitration in acetonitrile solution.

Product	With impure HNO_3[a]	With impure HNO_3 +1% urea	With freshly distilled HNO_3
Nitrodurene	45%	66%	72%
Acetoxydurene	2%	3%	3%
2,4,5-Trimethylbenzyl alcohol	25%	15%	12%
2,4,5-Trimethylbenzaldehyde	20%	9%	7%
2,4,5-Trimethylphenylnitromethane	8%	6%	6%

[a]Contained 5-10 times as much HNO_2 as freshly distilled nitric acid, by the Gries-Ilosvay test.

Table III

Dependence of products from durene on nitrous acid concentration - ratios on nitration in acetic acid solution.

Product	With impure HNO_3[a]	With impure HNO_3 +1% urea	With freshly distilled HNO_3
Nitrodurene	37%	49%	52%
Acetoxydurene	26%	34%	36%
2,4,5-Trimethylbenzyl alcohol	20%	9%	6%
2,4,5-Trimethylbenzaldehyde	12%	5%	3%
2,4,5-Trimethylphenylnitromethane	5%	3%	3%

[a]Contained 5-10 times as much HNO_2 as freshly distilled nitric acid, by the Gries-Ilosvay test.

Composition of reaction mixtures by N.m.r.

In each of the following tables (IV-VII) there is an error of ±2 in each figure due to the inaccuracies in estimating the N.m.r. integrals.

Table IV

N.m.r. analysis of o-xylene reaction (HNO_3/Ac_2O) before work-up

Product	In reaction mixture before heating	In reaction mixture after heating
4-Acetoxy-o-xylene	-	50
4-Nitro-o-xylene	36	34
3-Nitro-o-xylene	16	16
Dienes	48	-

Table V

N.m.r. analysis of hemimellitene reactions (HNO_3/Ac_2O) before work-up

Product	In reaction mixture before heating	In reaction mixture after heating
4-Nitrohemimellitene	46%	47%
5-Nitrohemimellitene	8%	9%
4-Acetoxyhemimellitene	8%	8%
5-Acetoxyhemimellitene	5%	36%
Dienes	33%	-

Table VI

N.m.r. analysis of p-xylene reaction (HNO_3/Ac_2O) before work-up.

Product	In reaction mixture before heating	In reaction mixture after heating
2-Nitro-p-xylene	20%	24%
2-Acetoxy-p-xylene	-	22%
p-Methylbenzyl acetate	14%	17%
p-Xylene	31%	37%
Dienes	35%	-

Table VII

N.m.r. analysis of 3-bromo-o-xylene reaction (HNO_3/Ac_2O) before work-up.

Product	In reaction mixture before heating	In reaction mixture after heating
6-Nitro-3-bromo-o-xylene	41%	40%
5-Nitro-3-bromo-o-xylene	3%	5%
4-Nitro-3-bromo-o-xylene	12%	12%
5-Acetoxy-3-bromo-o-xylene	-	23%
3-Bromo-o-xylene	19%	20%
Dienes	25%	-

Table VIII

Ratio of diene isomers in crude reaction mixtures of hydrocarbons with HNO_3/Ac_2O.

	o-Xylene	Hemimellitene	p-Xylene	3-Bromo-o-xylene
B/A (mole ratio)	1.73	1.83	2.80	1.77

Products of decomposition of dienes

Table IX

Products of decomposition of dienes from o-xylene and HNO_3/Ac_2O.

Diene isomer	Product on g.l.c. decomposition	Product on heating in acetic acid
A	4-acetoxy-o-xylene (100%)	4-acetoxy-o-xylene (100%)
B	4-acetoxy-o-xylene (100%)	4-acetoxy-o-xylene (100%)

Table X

Products of decomposition of dienes from hemimellitene and HNO_3/Ac_2O

Diene isomer	Product on g.l.c. decomposition	Product on heating in acetic acid
A	5-acetoxyhemi-mellitene (100%)	5-acetoxyhemi-mellitene (100%)
B	5-acetoxyhemi-mellitene (100%)	5-acetoxyhemi-mellitene (100%)

Table XI

Products of decomposition of dienes from p-xylene and HNO_3/Ac_2O.

Diene Isomer	Product	% formed on g.l.c. decomposition	% formed on heating in HOAc or OPr^-/HOPr
A	p-xylene	79%	24%
	2-acetoxy-p-xylene	21%	65%
	2-nitro-p-xylene	-	6%
	p-methylbenzyl acetate	-	5%
B	p-xylene	51%	16%
	2-acetoxy-p-xylene	49%	62%
	2-nitro-p-xylene	-	11%
	p-methylbenzyl acetate	-	11%

Table XII

Products of decomposition of dienes from 3-bromo-o-xylene and HNO_3/Ac_2O

Diene Isomer	Product	% formed on g.l.c. decomposition	% formed on heating in acetic acid
A	3-Br-o-xylene	96%	-
	5-acetoxy-3-Br-o-xylene	4%	100%
B	3-Br-o-xylene	96%	-
	5-acetoxy-3-Br-o-xylene	4%	100%

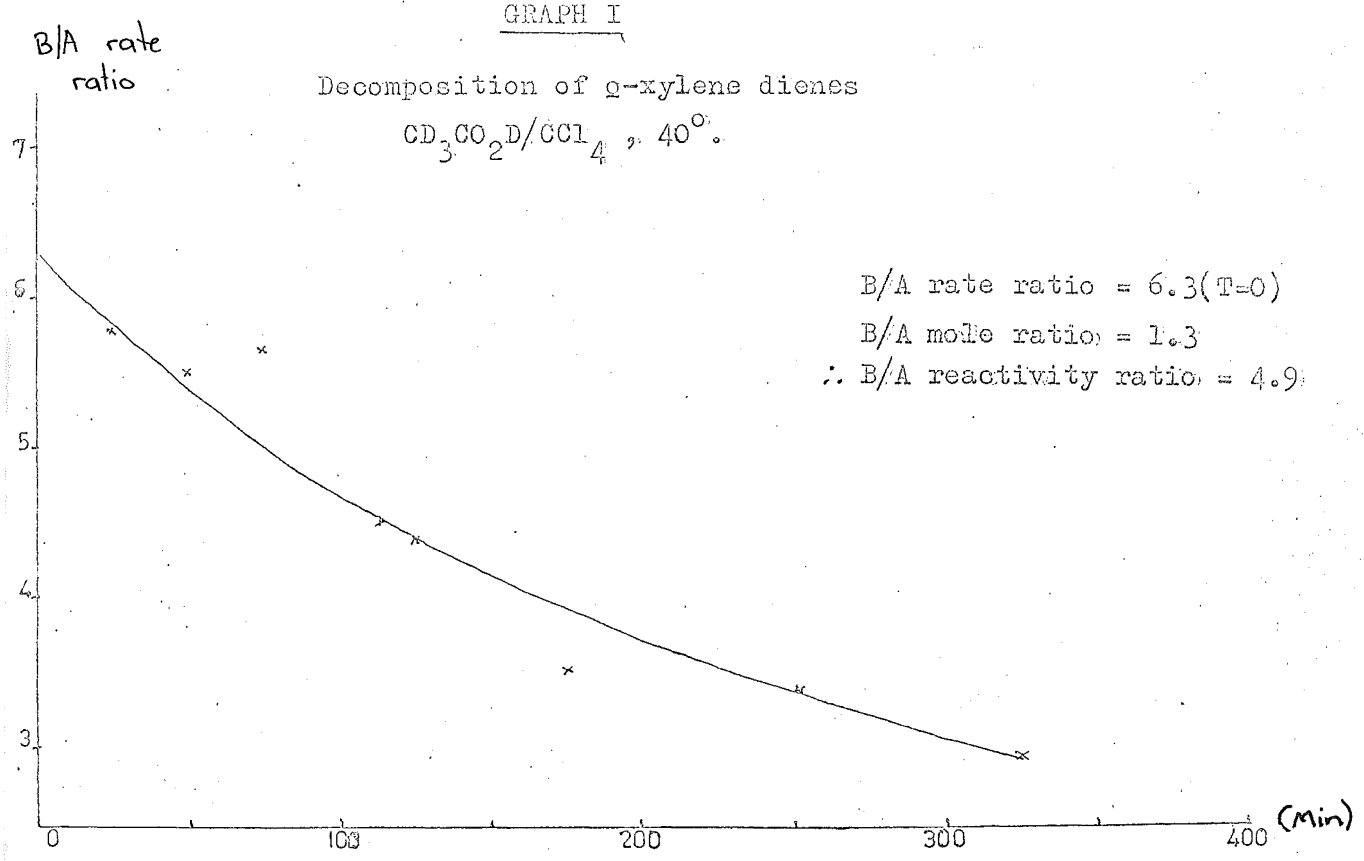
Competitive decomposition of diene isomers

Graphs I-III show the rate ratios of the diene isomer pairs from o-xylene, hemimellitene and p-xylene plotted against time. The values of the relative rates for the isomers A and B from these graphs are given in Table XIII. The results for the diene isomers from 3-bromo-o-xylene are not given, because, while decomposition eventually occurs, concurrent isomerization takes place. Results of

GRAPH I

Decomposition of p-xylene dienes

CD_3CO_2D/CCl_4 , 40°.



B/A rate ratio = 6.3(T=0)

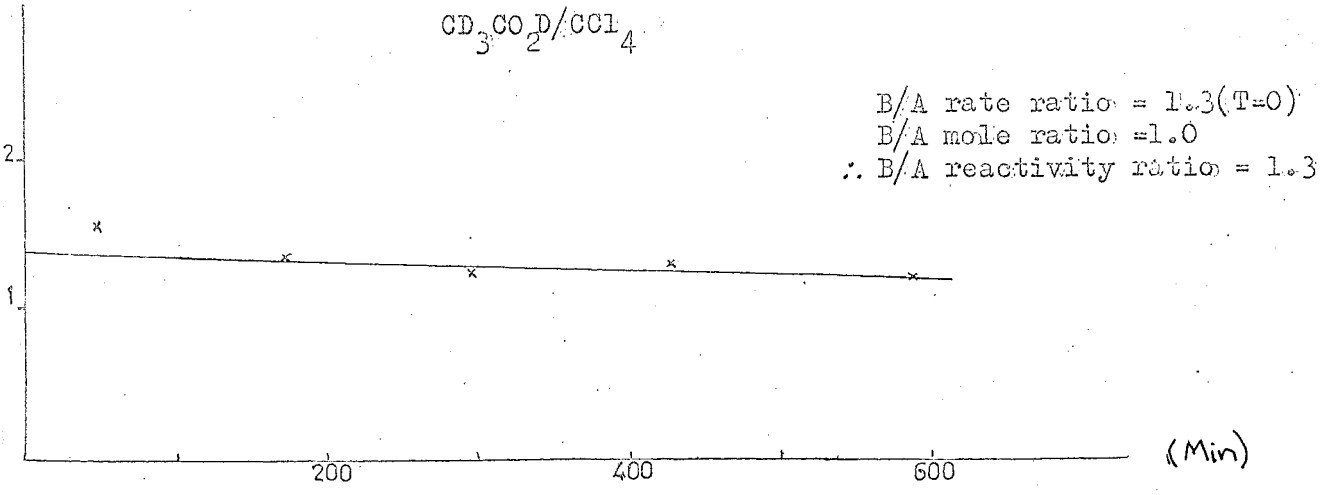
B/A mole ratio = 1.3

∴ B/A reactivity ratio = 4.9

GRAPH II

Decomposition of p-xylene dienes

CD_3CO_2D/CCl_4



B/A rate ratio = 1.3(T=0)

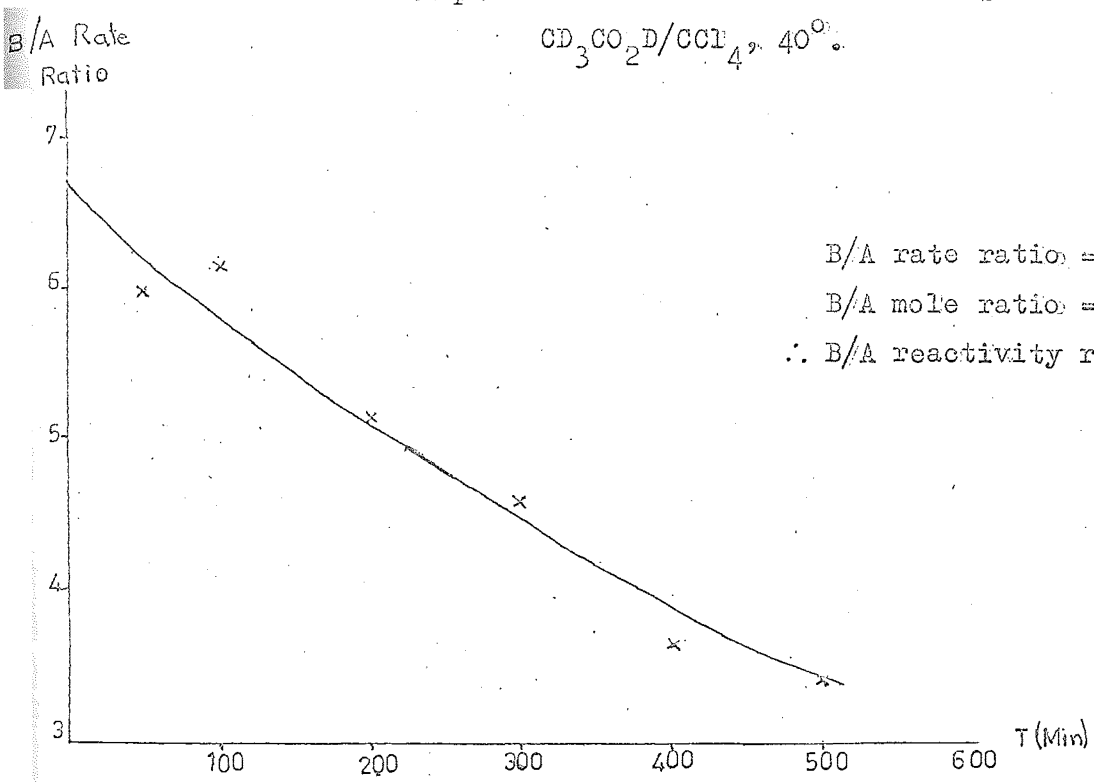
B/A mole ratio =1.0

∴ B/A reactivity ratio = 1.3

GRAPH III

Decomposition of hemimellitene dienes

CD_3CO_2D/CCl_4, 40°.



B/A rate ratio = 6.7 (T=0)

B/A mole ratio = 1.1

∴ B/A reactivity ratio = 6.1

Table XIII

Relative reactivities of diene isomers from aromatic substrates and HNO_3/Ac_2O.

	o-Xylene	Hemimellitene	p-Xylene
k_B/k_A	4.9	6.1	1.3

Table XIV

Decomposition in CD_3CO_2D at 20° of dienes from 3-Br-o-xylene and HNO_3/Ac_2O

T(hrs)	Diene B (N.m.r. integral units)	Diene A (N.m.r. integral units)
0	102	28
24	90	30.5
69	68	40
102	58	45.5
173	44	45
237	42	41
409	30	42.5

Kinetics of nitration by u.v. spectroscopy

Tables XV and XVI show results for typical runs for mesitylene and m-xylene, and graphs IV and V show first order rate plots for typical runs for mesitylene and m-xylene. Tables XVII and XVIII show the initial slopes obtained from the plots of the amount of product formed against time, together with the concentrations of hydrocarbon, for mesitylene and m-xylene. Table XIX summarizes the rate constants obtained from the first order rate plots for several different runs for m-xylene and mesitylene. In the tables, D is the absorbance of the solution, x the concentration of nitro-aromatic (moles/litre), A_o the initial concentration of hydrocarbon (moles/litre), and t the time of reaction (minutes).

Table XV

Nitration of mesitylene with HNO_3/Ac_2O in HOAc at 30°

D	$x \times 10^4$	$(A_o-x) \times 10^3$	$\log(A_o-x)+3$	t
.110	2.2	3.81	.581	5
.235	4.6	3.57	.553	10
.355	7.0	3.33	.522	15
.466	9.2	3.11	.493	20
.571	11.2	2.91	.464	25
.666	13.0	2.73	.436	30
.755	14.8	2.55	.407	35

A_o = [mesitylene] = 0.00403M; $[HNO_3]$ = 0.1945M; $[Ac_2O]$ = 0.885M.

Table XVI

Nitration of m-xylene with HNO_3/Ac_2O in HOAc at 30°

D	$x \times 10^4$	$(A_o-x) \times 10^3$	$\log(A_o-x)+3$	t
.057	0.7	5.30	.724	5
.097	1.2	5.25	.720	10
.138	1.7	5.20	.716	15
.179	3.2	5.15	.712	20
.223	2.7	5.10	.708	25
.265	3.2	5.05	.703	30
.309	3.7	5.00	.699	35
.350	4.2	4.95	.695	40
.436	5.3	4.84	.685	50
.518	6.3	4.74	.676	60

A_o = [m-xylene] = 0.00537M; $[HNO_3]$ = 0.1945M;
$[Ac_2O]$ = 0.885M.

Table XVII

Mesitylene concentration and slope of rate plot.

Mesitylene (moles/litre)	.0104	.0080	.0056	.0041	.0021
Slope	.831	.635	.450	.325	.164

$[HNO_3]$ = 0.1817M; $[Ac_2O]$ = 0.885M.

Table XVIII

m-Xylene concentration and slope of rate plot.

m-Xylene (moles/litre)	.0201	.0108	.0076	.0054	.0040
Slope	.327	.177	.125	.0885	.0650

$[HNO_3]$ = 0.1959M; $[Ac_2O]$ = 0.885M

Table XIX

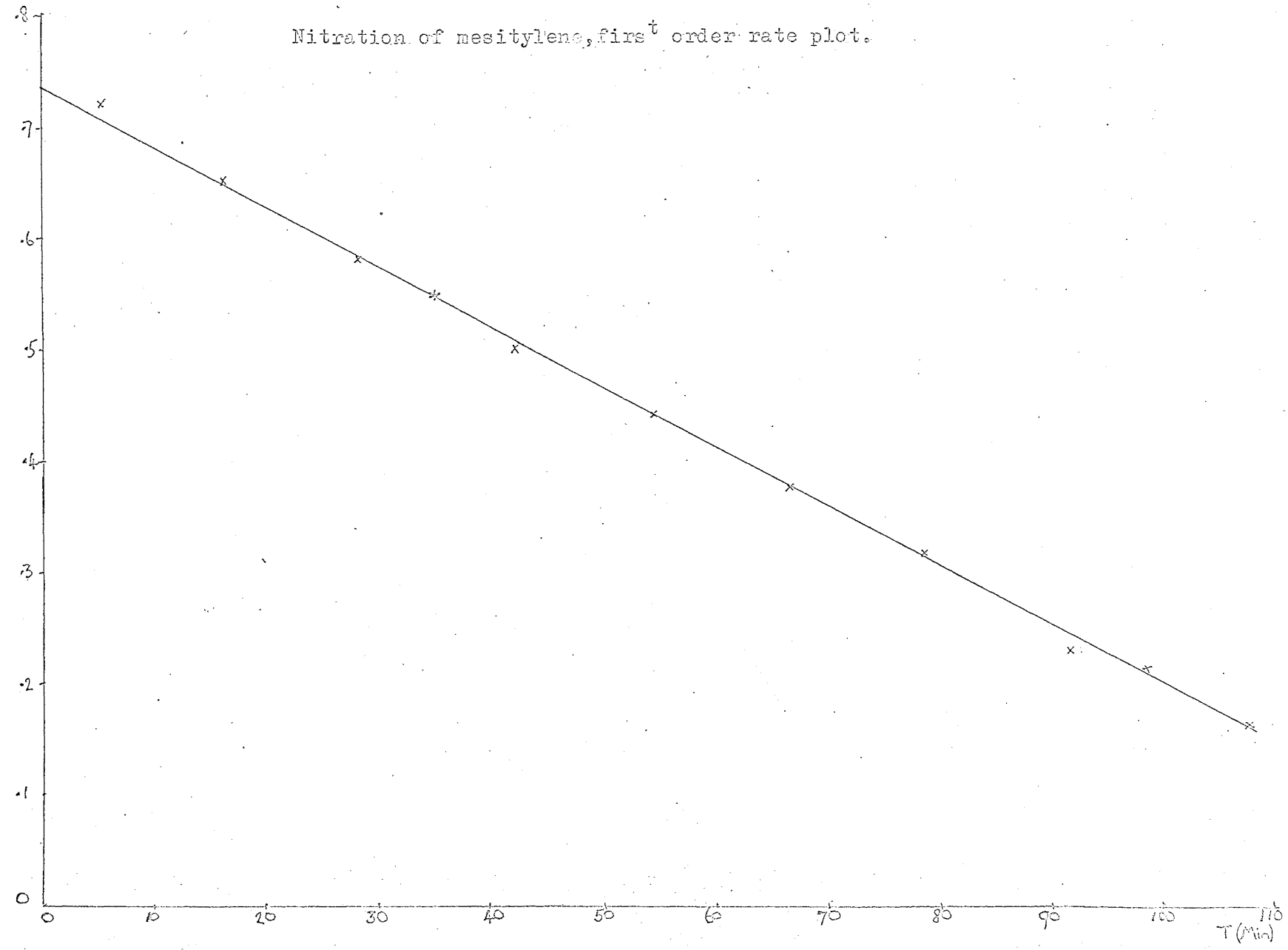
Rate constants[a] for nitration of mesitylene and m-xylene

m-xylene				mesitylene		
Run	A_o	$k \times 10^3 (min^{-1})$	$[HNO_3](M)$	Run	A_o	$k \times 10^3 (min^{-1})$
1	.00267	.952	.1893	1	.00460	5.53
2	.00491	1.051	.1942	2	.00438	5.87
3	.00537	.950	.1902	3	.00473	5.69
4	.00427	1.000	.1957	4	.00403	5.93
5	.00381	1.073	.1961	5	.00380	6.17

[a]These are not true rate constants, since the order of the reaction with respect to nitric acid and acetic anhydride is not known.

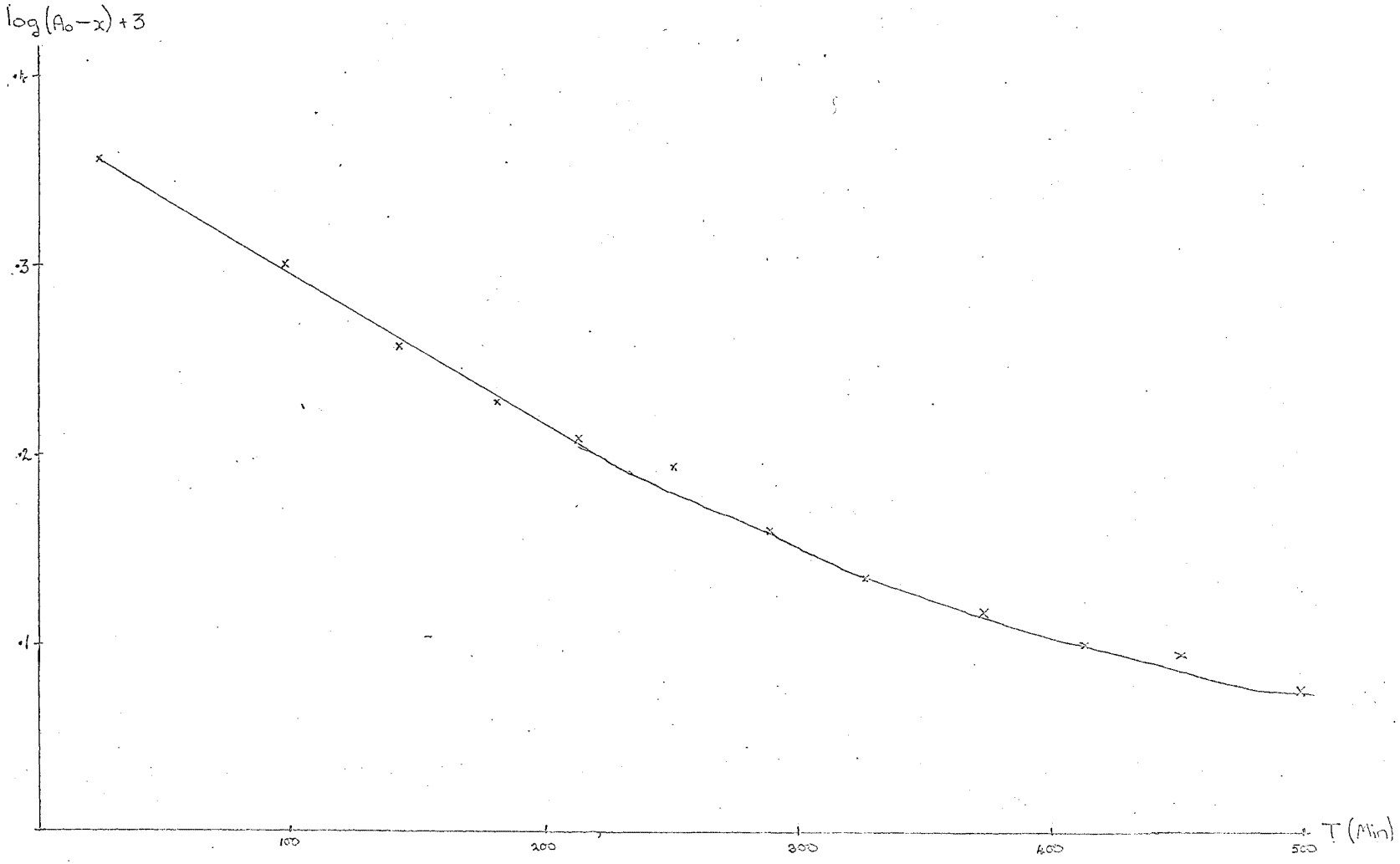
GRAPH IV

Nitration of mesitylene, first order rate plot.



GRAPH V

Nitration of m-xylene, first order rate plot.



Competitive nitrations

The graphs VI-VIII show typical runs for each of the hydrocarbon pairs used, with product ratios extrapolated back to zero time to give relative reactivities. Tables XX-XXIII show the data collected for the relative reactivities so obtained.

Table XX

Relative reactivities of m-xylene and mesitylene by competitive nitration with HNO_3/Ac_2O in HOAc

Run	m-Xylene(moles/litre)	Mesitylene(moles/litre)	$\frac{\text{Rate mesitylene}}{\text{Rate m-xylene}}$	$\frac{k(\text{mesitylene})}{k(\text{m-xylene})}$
1	.00532	.00463	5.57	6.4
2	.00526	.00388	4.06	5.5
3	.00411	.00451	6.47	5.9

Table XXI

Relative reactivities of m-xylene and o-xylene by competitive nitration with HNO_3/Ac_2O in HOAc

Run	o-Xylene(moles/litre)	m-Xylene(moles/litre)	$\frac{\text{Rate m-xylene}}{\text{Rate o-xylene}}$	$\frac{k(\text{m-xylene})}{k(\text{o-xylene})}$
1	.00504	.00552	1.70	1.55
2	.00478	.00503	1.81	1.72
3	.00518	.00463	1.43	1.61

Table XXII

Relative reactivities of o-xylene and toluene by competitive nitration with HNO_3/Ac_2O in HOAc

Run	o-Xylene(moles/litre)	Toluene(moles/litre)	$\frac{\text{Rate o-xylene}}{\text{Rate toluene}}$	$\frac{k(\text{o-xylene})}{k(\text{toluene})}$
1	.00498	.00552	6.3	7.0
2	.00527	.00915	3.6	6.3
3	.00527	.00798	5.1	7.7

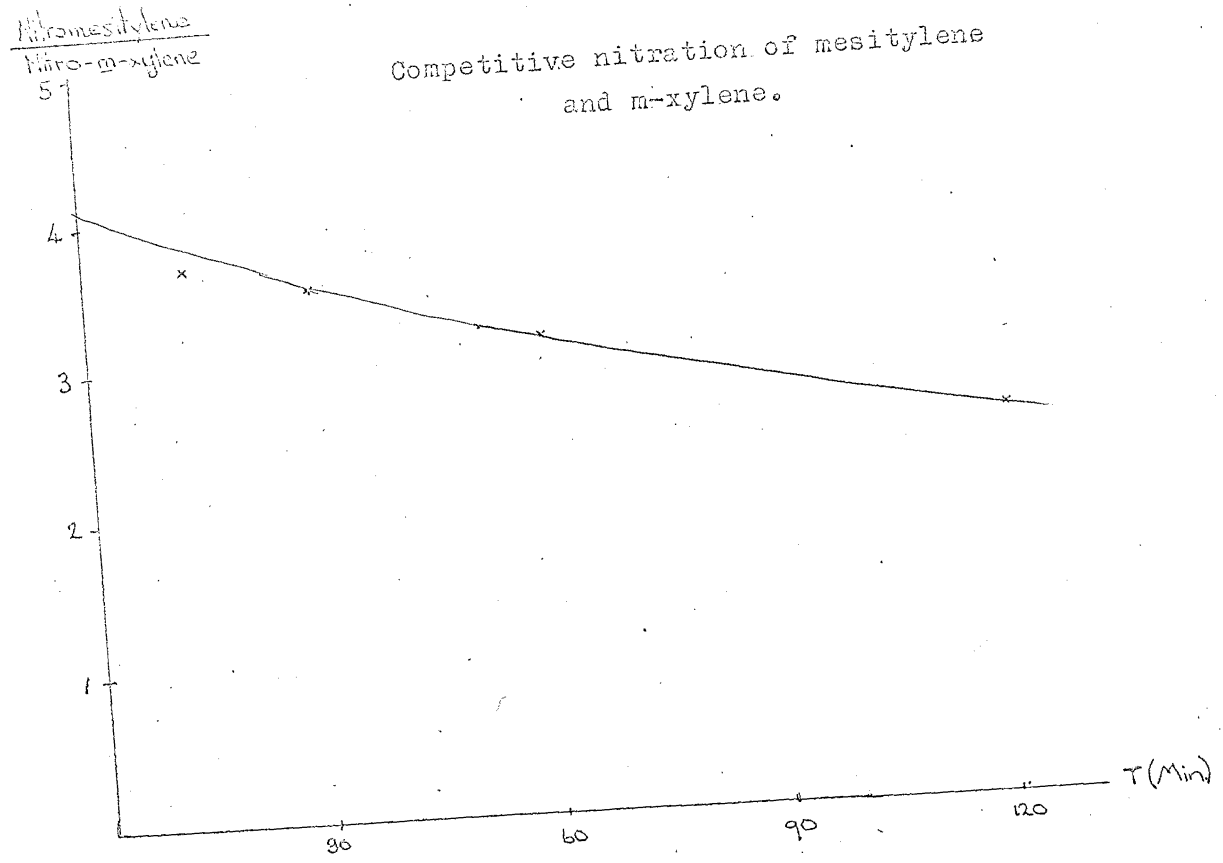
Table XXIII

Relative reactivities of toluene and benzene by competitive nitration with HNO_3/Ac_2O in HOAc.

Run	Toluene(moles/litre)	Benzene(moles/litre)	$\frac{\text{Rate toluene}}{\text{Rate benzene}}$	$\frac{k(\text{toluene})}{k(\text{benzene})}$
1	.00818	.0168	13.6	28.0
2	.00755	.0173	14.6	33.5
3	.00861	.0162	13.5	25.5

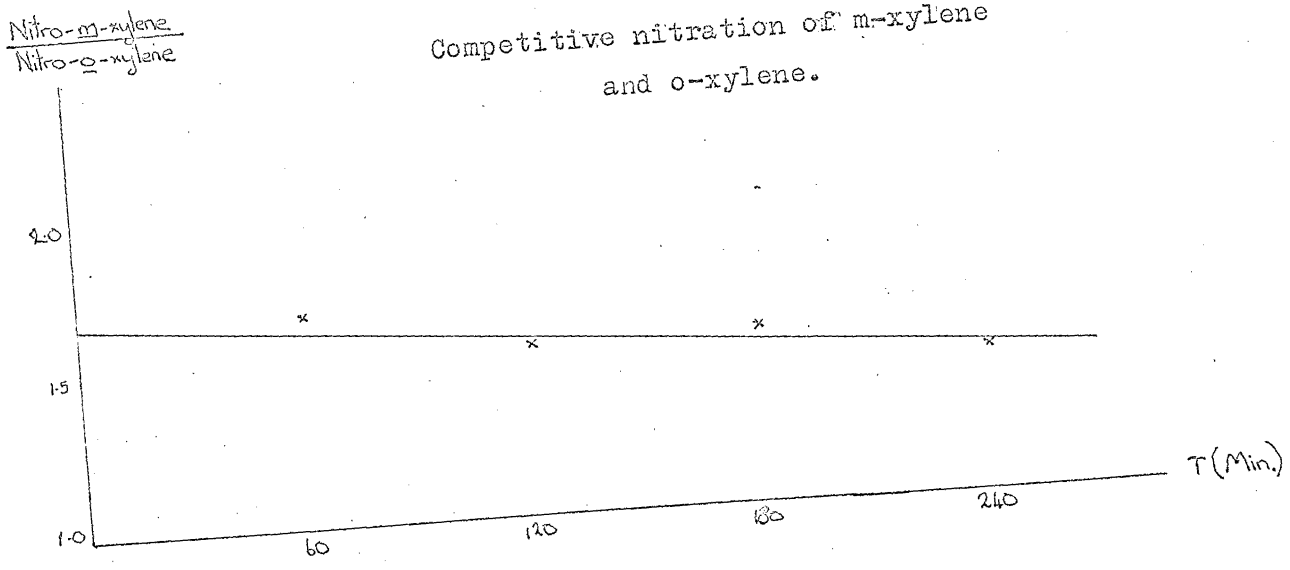
GRAPH VI

Competitive nitration of mesitylene and m-xylene.

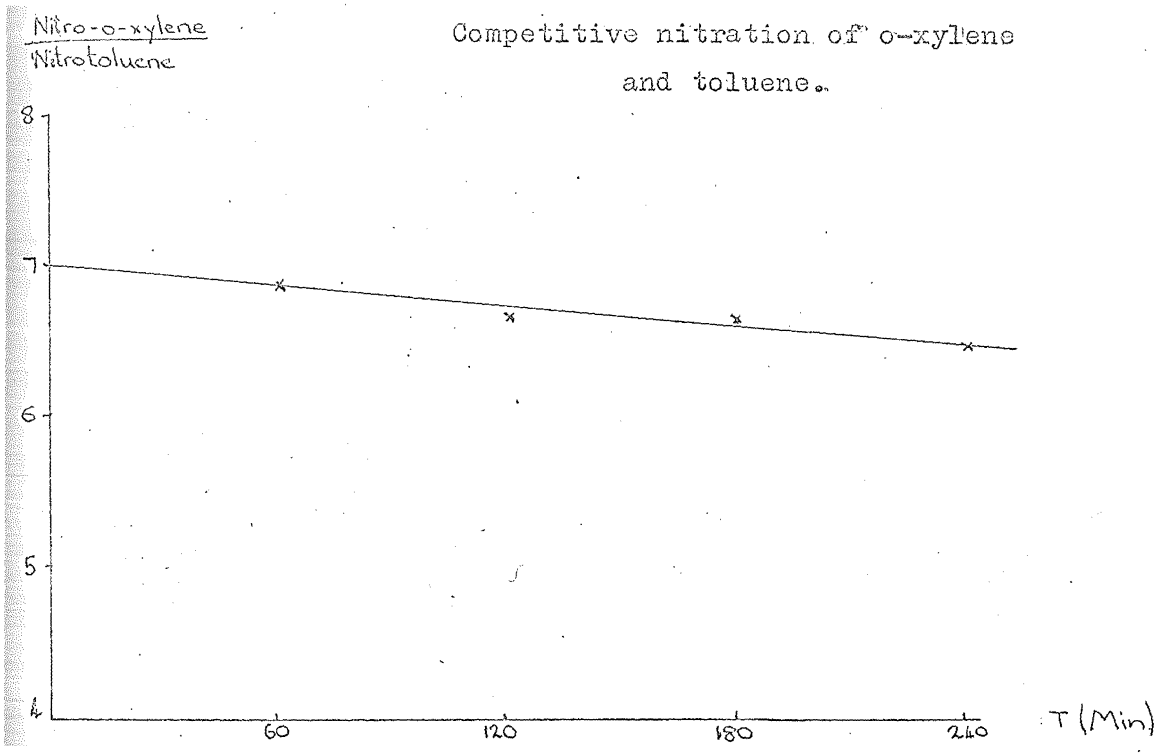


GRAPH VII

Competitive nitration of m-xylene and o-xylene.



GRAPH VIII


Nitro-o-xylene / Nitrotoluene
Competitive nitration of o-xylene and toluene.
8
7
6
5
4
60
120
180
240
T (Min)

Deuterium content of nitro-o-xylenes from deuterated o-xylenes

Table XXIV

Mass spectral analysis of 3- and 4-nitro-o-xylenes (undeuterated).

Isomer	Analysis	152 peak (cm)	151 peak (cm)	150 peak (cm)	151/152
3-nitro-o-xylene	1	0.55	5.20	-	9.46
	2	0.40	3.70	-	9.25
	3	0.30	2.70	-	9.00
	4	0.85	7.85	-	9.24
	5	0.70	6.65	-	9.36
4-nitro-o-xylene	1	0.65	5.90	-	9.09
	2	0.75	7.00	-	9.34
	3	0.40	3.80	-	9.50
	4	0.80	7.35	-	9.19
	5	0.30	2.80	-	9.33

Table XXV

Mass spectral analysis of nitro-o-xylenes from reaction of o-xylene-3-d with HNO_3/Ac_2O

Isomer	Analysis	153 peak (cm)	152 peak (cm)	151 peak (cm)
3-nitro-o-xylene	1	0.60	5.90	5.25
	2	0.70	7.55	6.80
	3	0.90	8.95	8.15
	4	0.35	4.00	3.60
	5	0.55	5.80	5.15
4-nitro-o-xylene	1	0.60	5.70	-
	2	0.65	5.90	-
	3	0.90	8.35	-
	4	0.80	7.65	-
	5	0.45	4.10	-

Table XXVI

Mass spectral analysis of nitro-o-xylenes from reaction of o-xylene-4-d with HNO_3/Ac_2O.

Isomer	Analysis	153 peak (cm)	152 peak (cm)	151 peak (cm)
3-nitro-o-xylene	1	0.80	7.60	-
	2	0.75	7.10	-
	3	0.50	4.45	-
	4	0.55	5.20	-
	5	0.75	6.75	-
4-nitro-o-xylene	1	0.75	7.60	6.95
	2	0.45	4.70	4.35
	3	0.65	6.60	5.90
	4	0.90	9.55	8.65
	5	0.80	8.55	7.70

From Table XXIV (analysis of undeuterated nitro-o-xylene isomers), the average M+1/M ratio is 9.275 (for $C_8H_9NO_2$ the M+1/M ratio should be[65] 9.249), with a spread from 9.00-9.46. From Tables XV and XXVI, the M+1/M ratio for 4-nitro-o-xylene from o-xylene-3-d ranges from 9.09 - 9.55, and for 3-nitro-o-xylene from o-xylene-4-d it ranges from 8.90 - 9.50. Within the errors of the analysis therefore, these substances have retained all the deuterium.

For 3-nitro-o-xylene from o-xylene-3-d, the 153 peak is M+1 from deuterated 3-nitro-o-xylene, the 152 peak is the parent peak (M) from deuterated 3-nitro-o-xylene plus the M+1 peak from undeuterated 3-nitro-o-xylene, and the 151 peak is the parent peak (M) from undeuterated 3-nitro-o-xylene. Therefore, for analysis 1:

$$\text{M (undeuterated material)} = 5.25 \text{ cm}$$

$$\therefore \quad \text{M+1 (undeuterated material)} = \frac{5.25}{9.275}$$

$$= 0.55$$

$$\therefore \quad \text{M (deuterated material)} = 5.90 - 0.55$$

$$= 5.35$$

$\therefore$ Deuterated 3-nitro-o-xylene:undeuterated 3-nitro-o-xylene

$$= 5.35:5.25$$

Table XXVII gives the ratios for other analyses worked out similarly, for 3-nitro-o-xylene from o-xylene-3-d, and 4-nitro-o-xylene from o-xylene-4-d. Within the errors of the analysis, this table shows 50% retention of deuterium in both cases.

Table XXVII

Deuterium retention in nitro-o-xylenes from deutero-o-xylenes.

Product	Analysis	Deuterated:undeuterated
3-nitro-o-xylene	1	1.02
from o-xylene-3-d	2	1.01
	3	0.99
	4	1.00
	5	1.02
4-nitro-o-xylene	1	1.02
from o-xylene-4-d	2	1.00
	3	0.98
	4	1.02
	5	0.97

Table XXVIII

Nitration of o-xylene by HNO_3/Ac_2O (1:1) in chloroform at -20°

	4-acetoxy-o-xylene	4-nitro-o-xylene	3-nitro-o-xylene
No additive	7%	61%	32%
With 0.5 equiv. Ac_2O added	11%	58%	31%
With 1 equiv. Ac_2O added	16%	55%	29%
With 0.5 equiv. HOAc added	13%	57%	30%
With 1 equiv. HOAc added	17%	54%	29%

DISCUSSION

This discussion deals with various aspects of the reaction of aromatic substrates with nitric acid-acetic anhydride. It is divided into five main sections - the acetoxylation reaction, and the diene intermediates involved in acetoxylation; the mechanism of formation of phenylnitromethane and aldehyde products; the formation of nitrophenols, and the cyclohexadienone intermediates leading to these products; the nature of the nitration reaction; and the occasional formation of other types of products.

Diene Intermediates in Acetoxylation

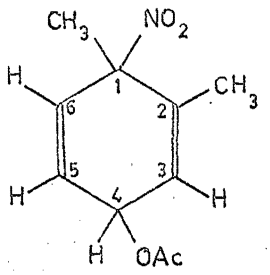
The formation of aryl acetates from aromatic substrates and nitric acid-acetic anhydride has been found to occur via the prior formation of acetoxy-nitro adducts, which eliminate nitrous acid to give the aryl acetates. These dienes, and the mechanisms of their formation and decomposition are discussed in this section.

(1) Structure of the dienes

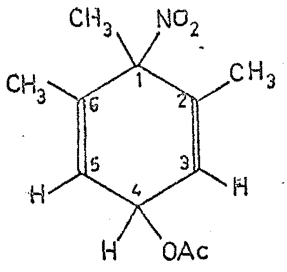
The dienes are sufficiently similar in structure to be all discussed together. The presence of both nitro and acetoxy groups is established by the I.R. spectra, which have bands at 1730-1740 and 1215-1240 cm^{-1} (acetoxy

group[72]), and at 1540-1545 and 1340-1365 cm^{-1} (non-aryl nitro group[72]). That the compounds are dienes and not aromatic molecules is established by the positions of the ring protons (δ = 5.5-6.2 ppm) and methyl protons (δ = 1.45-1.9 ppm) in the N.m.r. spectra[66]. The u.v. spectra (λ_{max} = 195-210 nm) indicate a 1,4 diene structure, and not a 1,3 diene structure which would be expected to absorb at higher wavelengths, above 250 nm[72].

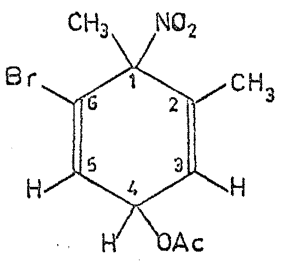
These considerations, together with the chemical behaviour of the dienes, point to cis and trans isomers of the structures I-IV as the most reasonable ones for the dienes from o-xylene, hemimellitene, 3-bromo-o-xylene and p-xylene respectively. The cis-trans isomerism is dealt with more fully in the next section; the N.m.r., I.R. and u.v. spectra of each isomer pair are so similar as to preclude any other interpretation. The structures



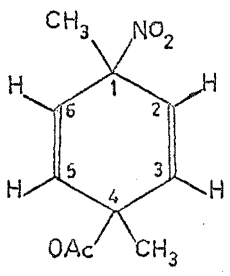
I



II

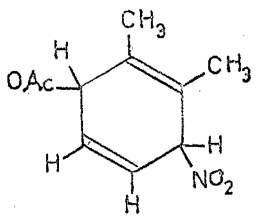


III

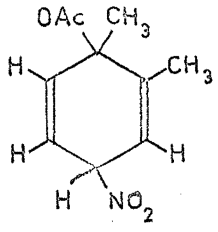


IV

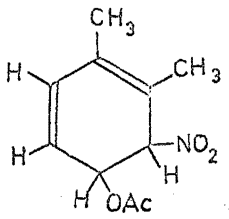
are consistent with the physical evidence; they are also consistent with the decomposition (for I, II and III) solely into one acetate product, since elimination of HNO_2 should take place readily and no simple corresponding elimination of HOAc to give a nitro product is available. In the case of o-xylene, for example, the alternative 1,4 diene structures are V and VI. Both V and VI require acetate migrations to give the observed acetate products, though this does not necessarily rule them out, as similar migration is observed for the diene isomers from p-xylene. Both, however, should be able to eliminate HOAc to give a nitro-o-xylene; this would be expected to be the major product from VI and perhaps also from V, in view of the known acidity of the α-hydrogen in aliphatic nitro compounds. 1,3-dienes of the type VII would also be expected to eliminate HOAc very readily, particularly in base, because of the acidity of the hydrogen α to the nitro group. The absence of nitro-aromatics in the decomposition products of the dienes (Tables IX, X, XII), therefore, is evidence for the structures assigned.



V



VI



VII

The details of the N.m.r. spectra (Tables XXIX and XXX) also point almost certainly to the structures I-IV. In these tables, and in subsequent discussion, diene A refers to the more stable of a pair of isomers, and B to the less stable. The sizes of the coupling constants are reasonable for the protons to which they are assigned, and difficult to account for on the basis of any other structure. For example, for both the diene isomers from o-xylene, one singlet and one triplet are observed for the methyl groups. Any structure such as V or VII, in which both methyl groups are attached to unsaturated carbon atoms, cannot account for this, since at least some coupling would be expected for the second methyl in view of the fact that coupling to similarly placed protons occurs for the first methyl group. Similar comments apply to the dienes from hemimellitene and 3-bromo-o-xylene. In addition, the coincidence of the N.m.r. peaks for C^2H_3 and C^6H_3, and for H^3 and H^5 (which is expected from the symmetry of the molecule) is confirmatory evidence of the structure in the case of hemimellitene, as is the shift downfield of the H^5 resonance (caused by the adjacent bromine atom[73]) in the case of 3-bromo-o-xylene.

p-Xylene is a slightly different case, but structure IV is supported by analogy with the other dienes, by the identical chemical shifts of the ring protons and by the

Table XXIX

Chemical shifts (δ) of dienes from acetoxylation of aromatic substrates.

Diene		Chemical Shift					
		C^1H_3	C^2H_3	H^3	H^4	H^5	H^6
Hemimellitene	A	1.68	1.76	5.79	5.53	5.79	-
	B	1.77	1.79	5.82	5.65	5.82	-
o-xylene	A	1.70	1.78	5.85	5.54	6.01	6.01
	B	1.78	1.83	5.86	5.72	6.03	6.03
3-Br-o-xylene	A	1.82	1.82	1.80	5.80	5.56	6.50
	B	1.91	1.91	1.82	5.82	5.76	6.50
		C^1H_3	C^4H_3	H^2	H^3	H^5	H^6
p-xylene	A	1.67	1.53	6.21	6.21	6.21	6.21
	B	1.76	1.45	6.03	6.03	6.03	6.03

Table XXX

Coupling constants (Hz) of protons in dienes from acetoxylation of aromatic substrates.

Diene		Coupling constants				
		C^2H_3-H^3	C^2H_3-H^4	H^3-H^4	H^4-H^5	H^3-H^5
Hemimellitene	A	0.5	1.5	2.5	2.5	-
	B	0.5	1.0	4.0	4.0	-
o-xylene	A	1.0	1.5	2.0	2.0	-
	B	1.0	1.0	2.5	2.5	-
3-Br-o-xylene	A	1.0	1.0	3.5	3.5	1.5
	B	1.0	1.0	-	4.0	2.0
p-xylene	A	No coupling				
	B	No coupling				

lack of coupling of the ring protons to either of the methyl groups. The absorption of the second methyl group (1.45 and 1.53 ppm), which is geminal to the acetate group, is considerably upfield from any methyl group in the other dienes, showing that it is in an environment different to any in these other cases.

(2) Cis-trans isomerism of dienes

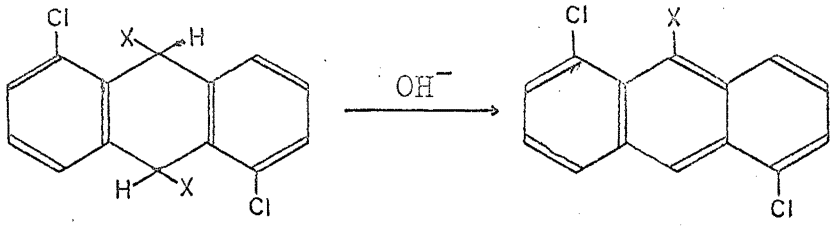
The results of competitive decompositions in acetic acid of the diene isomers show that in each case isomer B is the more reactive under the conditions used. Table XXXI gives the relative reactivities of the isomers from o-xylene, hemimellitene and p-xylene. The reactivity ratio of the dienes from 3-bromo-o-xylene is not included in this table because during the decomposition it was evident that isomerization was also taking place; the amount of isomer A present began to increase during the reaction, while the amount of isomer B decreased, and the amount of aromatic acetate also increased (Table XIV). Eventually the amount of isomer A also began to decrease, but since there were two reactions taking place it was not possible to estimate the relative reactivities of the two dienes in this case. However, as on prolonged heating in acetic acid the mixture of two dienes could be converted to a mixture of aromatic acetate and isomer A only, it appears that in this case also isomer A is the more stable.

Table XXXI

Relative reactivities of diene isomers

	o-xylene	hemimellitene	p-xylene
k_B/k_A	4.9	6.1	1.3

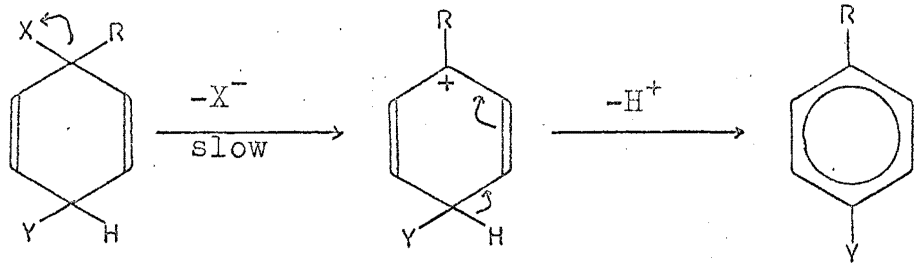
Cristol et al have studied[74] the base-catalyzed decompositions of cis- and trans- 1,5-dichloro-9,10-dihydro-9,10-anthradiols, and their diacetates or dibenzoates, to 9-substituted anthracene derivatives.



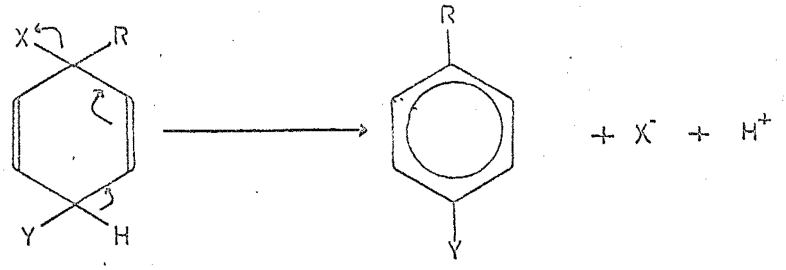
X = OH, CO_2Me, CO_2Ph.

They found that in each case the trans isomer reacted faster by at least a factor of 10^2-10^3, and since the systems resemble one another, these results should probably also apply to the cyclohexadiene isomers studied in the present work. It is therefore concluded that in each case

the isomer designated A is probably the cis isomer, and B the trans isomer. There is a much smaller difference in reactivity between any two isomeric dienes from the present work, than between Cristol's isomeric compounds. This difference is a reasonable one when it is considered that in the anthracene system positive charge is being developed on a secondary carbon atom, whereas it is being developed on a tertiary centre in the dienes studied here. This difference is likely to lead to at least some change in the mechanism of the elimination. In the extreme case of an E_1 mechanism, a full carbonium ion is formed in the slow step, and this should lead to no distinction between isomers, since reaction is not affected by the geometry at C^4.



In a concerted mechanism, on the other hand, participation by the proton at C^4 could lead to a preferential decomposition of one of the isomers.

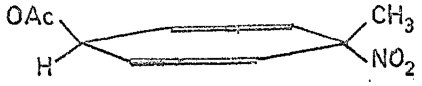


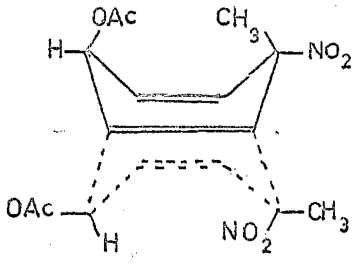
Between these extremes there is a continuous range of possibilities with differing degrees of positive charge developed on C^1. When R = Me (the present work) positive charge is being developed on a tertiary centre; when R = H (Cristol's work), any positive charge will be less stabilized since it is being developed on a secondary centre. This should lead to a more concerted reaction in the anthracene systems, and to the observed larger differentiation between isomers. In addition, Cristol's reactions were base-catalyzed, and a concerted mechanism would be aided by base attack on the proton being eliminated.

Some confirmation of the assignments of A as the cis isomer and B as the trans isomer comes from the chemical shifts of the C^1 methyl group and the C^4 proton (Table XXIX) in the N.m.r. spectra of the dienes from o-xylene, hemimellitene and 3-bromo-o-xylene. In each case these absorptions are at lower field in the B isomer than in the A isomer, whereas there is little difference between two isomers in the positions of other absorptions. Both the nitro and acetate groups will deshield protons close to

them[75], and these differences are explicable if it is assumed that the nitro group is, in the trans isomer, deshielding the C^4 proton (which is cis to it) relative to the cis isomer (in which the two are trans, and consequently further apart). Similarly, the acetate group is deshielding the C^1 methyl in the trans isomer relative to the cis isomer, also causing a shift to lower field.

The dienes from p-xylene do not fit into this picture. The C^1 methyl resonance in isomer B is downfield relative to A; however, the C^4 methyl absorption which should also shift downfield has in fact moved upfield. The interpretation of the N.m.r. changes in terms of deshielding by the nitro and acetate groups requires either that the dienes be planar (and this is the preferred conformation of cyclohexa-1,4 dienes[76]) or that, if the molecules are in the boat conformation, the two boat forms be interconverting so fast that the observed spectrum is a time-averaged one. It may





be that this assumption is not justified in the case of the dienes from p-xylene. However, it is noticeable that the

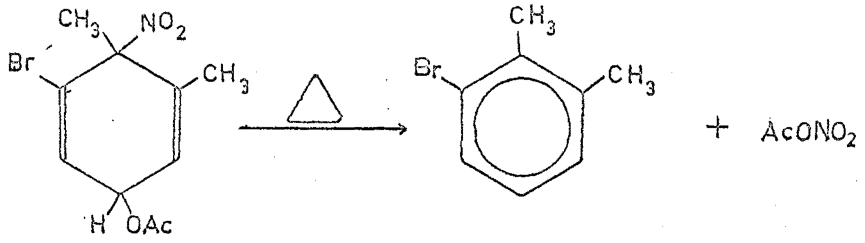
two isomers have very nearly the same reactivity in acid-catalyzed decomposition in the p-xylene case; in view of this and the conflict in the N.m.r. spectra, the assignments here of A as the cis isomer and B as the trans isomer must be regarded as more doubtful than in the other cases.

(3) Decomposition products of dienes

(a) Hemimellitene and o-xylene. Both isomers of the dienes from these substrates decompose, either on standing in acetic acid, or on injection onto a g.l.c. column, entirely into a single acetoxy-substituted product, 5-acetoxyhemimellitene and 4-acetoxy-o-xylene respectively (Tables IX and X). The decompositions are, therefore, simple eliminations of HNO_2, as would be expected.

(b) 3-Bromo-o-xylene. Both isomers of the diene from this substrate also decompose by elimination of HNO_2 into the expected product (5-acetoxy-3-bromo-o-xylene) on heating with acetic acid, and this is the only aromatic product formed (Table XII). The decompositions are, however, very much slower than those of the corresponding dienes from hemimellitene and o-xylene. The half-life of even the less stable isomer (B) from 3-bromo-o-xylene in acetic acid at 20° was at least 120 hours; the half-life of the more stable isomer (A) from the other substrates was 4-5 hours under these conditions. This difference can

probably be attributed to the inductive effect of the bromine atom on C^6 destabilising the positive charge which develops on C^1 during the elimination. The slowness of this decomposition allows isomerization (B to A) to become competitive; as has been noted (Table XIV), both isomerization and decomposition take place in acetic acid. It also allows the alternative reaction of elimination of acetyl nitrate with reversion to starting material to take place on a gas chromatography column; both isomers give 96% 3-bromo-o-xylene and only 4% 5-acetoxy-3-bromo-o-xylene on g.l.c. (Table XII). This is why such small quantities



(2%) of 5-acetoxy-3-bromo-o-xylene are present when the reaction mixture is analyzed by g.l.c., although much larger quantities (31%) of diene are present when the mixture is analyzed by N.m.r. These dienes are sufficiently stable to survive the work-up procedure preceding g.l.c. analysis, and therefore show up largely as starting material.

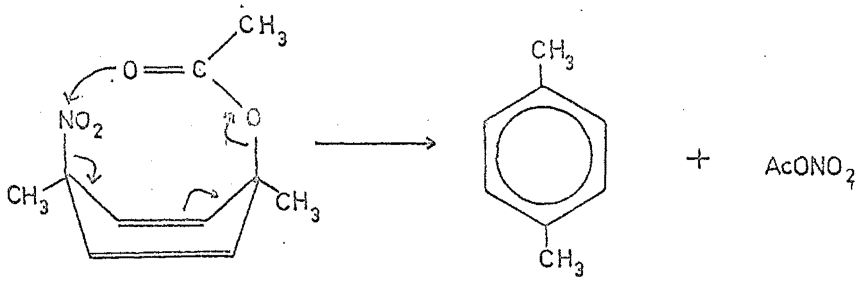
(c) p-Xylene. Two paths of decomposition are evident for each diene isomer, both in acetic acid and on a gas

chromatography column - the elimination of acetyl nitrate to regenerate p-xylene, and the elimination of nitrous acid, and migration of the acetate group, to give 2-acetoxy-p-xylene (Table XI).

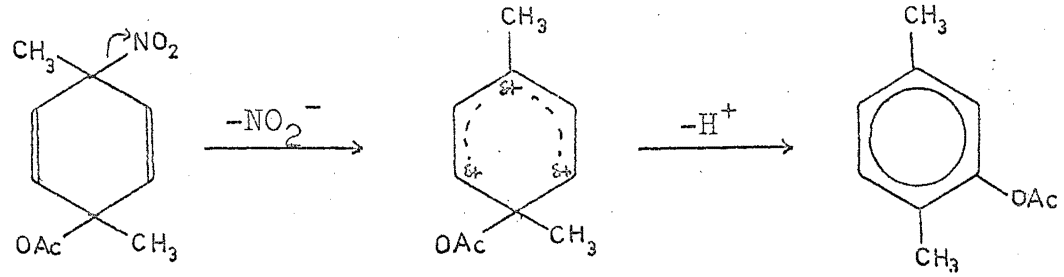
Since the formation of acetoxylated product is not a straightforward elimination, but also involves acetate migration, it is not surprising that elimination of acetyl nitrate becomes significant for the dienes from p-xylene, but not for those from hemimellitene and o-xylene. Thus in acetic acid, only 60-65% of the dienes decompose to 2-acetoxy-p-xylene; the remainder of the products consist of p-xylene, 2-nitro-p-xylene, p-methylbenzyl acetate (Table XI). These latter two products are known to be formed directly from the nitration of p-xylene with HNO_3 in acetic anhydride, since they are present in the reaction mixture before any decomposition of the dienes occurs. Almost certainly, therefore, they are formed during the decomposition of the dienes in acetic acid by further reaction of the liberated p-xylene and acetyl nitrate.

On g.l.c. analysis, decomposition of the p-xylene dienes to p-xylene rather than 2-acetoxy-p-xylene occurs to a greater extent than in HOAc. Diene A gives a higher ratio of p-xylene to 2-acetoxy-p-xylene (79:21) than does diene B (51:49), and this provides some support for the formulation of A as the cis isomer, since preferential elimination of

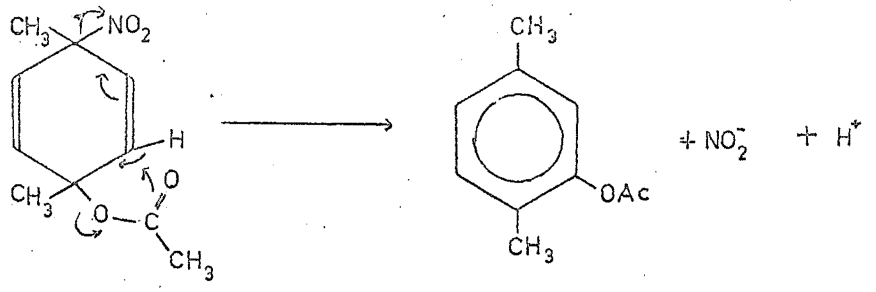
of acetyl nitrate might be expected via a cyclic transition state such as has been proposed to account for preferred 1,4 cis eliminations in other thermal reactions[74].

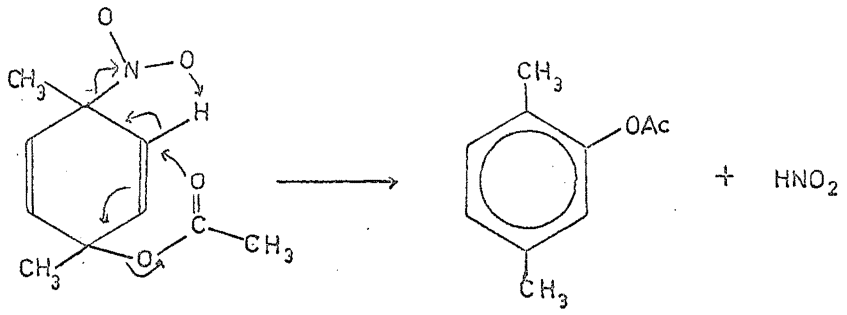


The second mode of decomposition, to 2-acetoxy-p-xylene, requires a rearrangement of the acetate group. This rearrangement is almost certainly intramolecular, since decomposition in propionic acid, or in a saturated solution of sodium propionate in propionic acid did not lead to any incorporation of propionate. However, it is not certain whether this is a 1,2 or 1,3 rearrangement. In a two-step mechanism, 1,2 rearrangement will be favoured because of the positions of the positive charge in the carbonium ion.

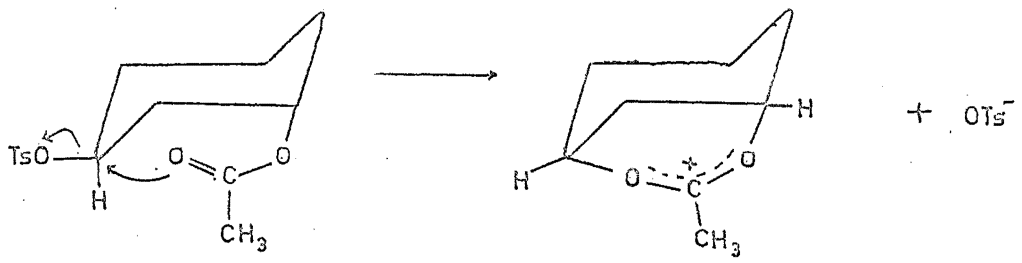


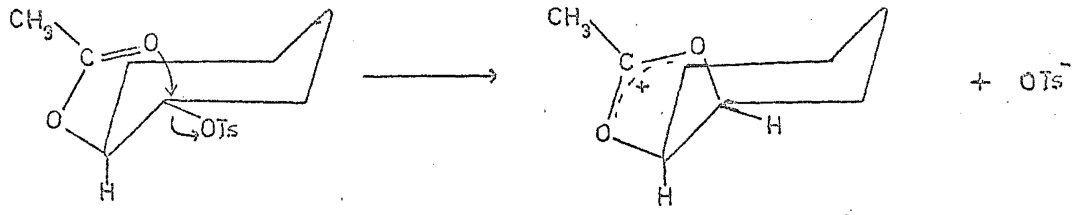
On the other hand, in a one-step rearrangement, 1,3 migration may be more favourable because the leaving nitrite group could assist the removal of the proton from the ring.





The situation somewhat resembles the formation of acetoxonium ions in certain substitution reactions in cyclohexane systems[77]. There, it is found that either 1,2 or 1,3 shifts can occur depending upon the geometrical relationships of the reacting groups:





For the p-xylene dienes, inspection of models shows that if the cyclohexadiene ring is planar (and this is the preferred conformation of a cyclohexa-1,4-diene[76]), then a 1,3 acetate shift is unlikely. However, the planar form of the cyclohexadiene ring is not of very much lower energy than the alternative boat form[76], and could easily convert into it. In the boat form, the carbonyl oxygen of the acetate group could come into the required position for a 1,3 rearrangement.

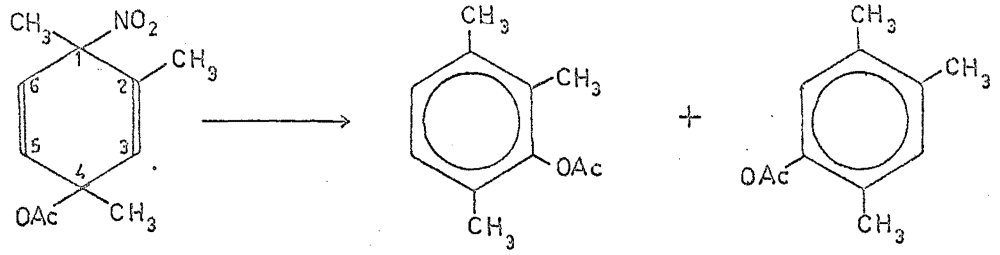
Wright[7] has examined the products and product ratios of a number of methyl-substituted benzenes with nitric acid-acetic anhydride; his results are given in Table XXXII. From pseudocumene he obtained 5-acetoxypseudocumene and 3-acetoxypseudocumene (in the ratio 2.6:1), but no 6-acetoxypseudocumene. This is consistent with a 1,2 acetate rearrangement from the expected diene intermediates VIII, with the preponderance of 5-acetoxy product resulting either from the steric hindrance of the 2-methyl group, or the reduced acidity of the proton on C^3 due to this methyl

Table XXXII

Product distribution from the reactions of hydrocarbons with nitric acid/acetic anhydride.

Hydrocarbon	Product	Percentage
Toluene	o-nitrotoluene	58%
	m-nitrotoluene	3%
	p-nitrotoluene	36%
	p-acetoxytoluene	3%
o-Xylene	3-nitro-o-xylene	50%
	4-nitro-o-xylene	33%
	3-nitro-o-xylene	17%
m-Xylene	2-nitro-m-xylene	14%
	4-nitro-m-xylene	85%
	4-acetoxy-m-xylene	1%
Hemimellitene	4-nitrohemimellitene	46%
	5-nitrohemimellitene	8%
	4-acetoxyhemimellitene	11%
	5-acetoxyhemimellitene	35%
Pseudocumene	3-nitropseudocumene	10%
	5-nitropseudocumene	50%
	6-nitropseudocumene	4%
	3-acetoxypseudocumene	10%
	5-acetoxypseudocumene	25%

group. A 1,3 acetate migration would give 6-acetoxypseudocumene only.

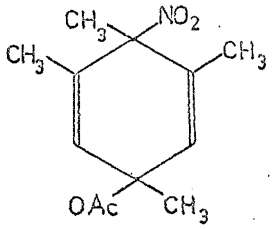


VIII

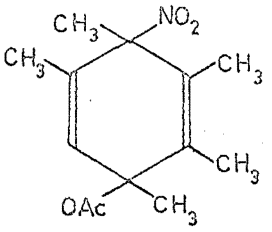
Unfortunately, attempts to confirm this by isolation of the intermediate VIII failed. A repetition of Wright's work under apparently identical conditions not only gave no evidence by N.m.r. for the formation of VIII but also failed to give more than a small amount (3%) of acetoxy product. Instead, large quantities of 3,4-dimethylphenylnitromethane were isolated.

On the other hand, results obtained in the present work for the nitration of isodurene and pentamethylbenzene can be interpreted in terms of a 1,3 acetate shift; isodurene gives 5%, and pentamethylbenzene 0%, acetoxy products. Since the intermediates for acetate formation (IX and X) are blocked from 1,3 acetate rearrangements, but not from 1,2 rearrangements, this would be the expected result if 1,3 migration was the normal route. These results (nitration of pseudocumene, isodurene and pentamethylbenzene) will be discussed later (p.132) in greater detail; it seems,

however, that the lack of acetate from isodurene and pentamethylbenzene can be accounted for in other ways, and that Wright's results, therefore, favour a 1,2 acetate migration.



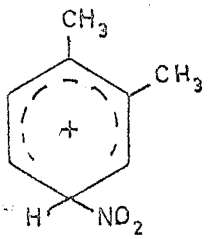
IX



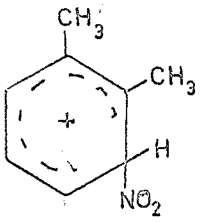
X

(4) Mechanism of formation of dienes

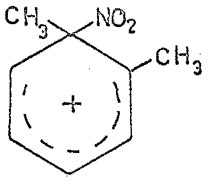
The presence of the nitro group attached to a tertiary carbon atom in the cyclohexadienes indicates that initial reaction is almost certainly an electrophilic attack on the aromatic ring. In addition to the attack on an unsubstituted ring position with the formation of "normal" Wheland intermediates XI and XII (from o-xylene), attack also occurs on a carbon atom bearing a methyl group, to give the Wheland intermediate XIII. Unlike XI and XII, XIII cannot rearomatize simply by loss of a proton; it will therefore



XI

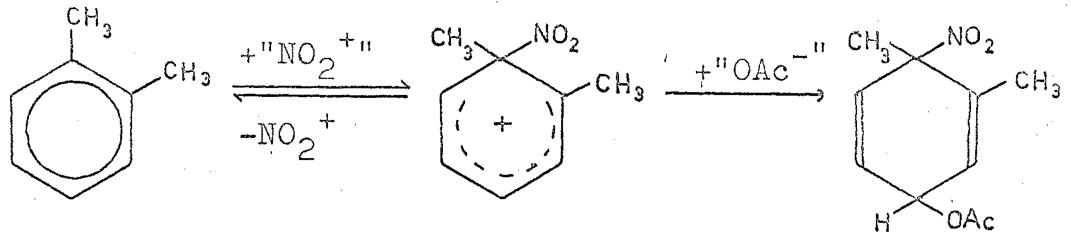


XII



XIII

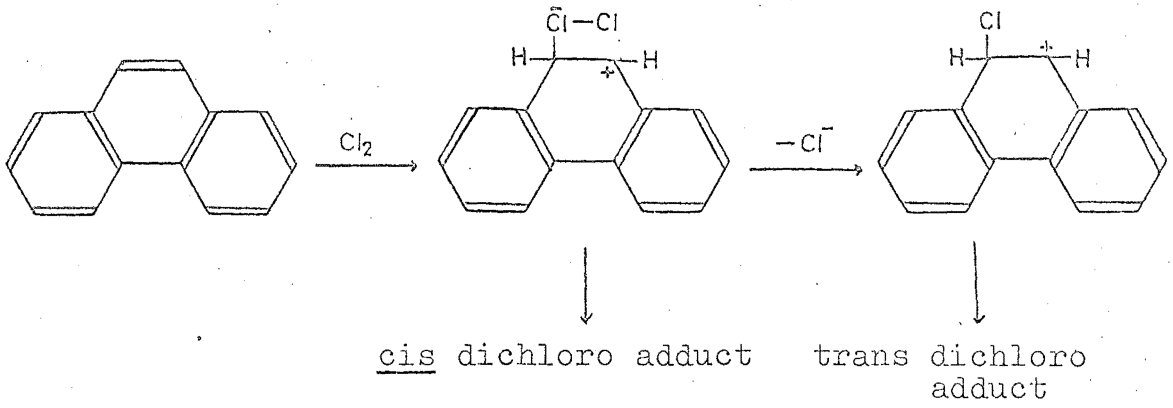
decompose by the reverse reaction (loss of NO_2^+), or add acetate in the para position to give a diene. The proposed mechanism is therefore



The identity of the nitrating species in the first step of this mechanism is discussed later (p. 152). A full investigation of the species responsible for the acetoxylation in the second step was not undertaken in this work, but some conclusions can be drawn from results which are available, mainly for o-xylene.

If the nitrating species is protonated acetyl nitrate, the acetic acid molecule liberated during the nitration step may never be completely released from the carbonium ion (XIII). Instead, it could immediately take part in the addition step to form the diene. Such a mechanism would lead to a cis diene only, and cannot account for the trans diene isomers - N.m.r. analyses of the reaction mixtures (Table VIII) show that, in fact, the trans isomer predominates in all cases. While this rules out the formation of

all the diene from such a cis collapse of an ion pair, it is possible that this is the mode of formation of the cis isomers. De la Mere et al have concluded[8b,13] that in the formation of dichloro adducts from phenanthrene, and tetrachloro adducts from naphthalene, cis addition is determined at an early stage of the reaction, while trans addition comes at a later stage and perhaps through a different intermediate. Thus a possible reaction path for phenanthrene is:



cis dichloro adduct trans dichloro adduct

(+ other products)

In the case of the dienes formed in the present work, that portion of the dienes which does not come from this cis addition, could come from nucleophilic attack of acetyl nitrate, acetic acid, or acetic anhydride at the second step. There is some evidence that each of these may be the nucleophile, though sometimes not very satisfactory evidence, owing to the difficulty of rigorously ruling out the presence of more than one of these entities.

The nitration of o-xylene with mixed acid in acetic acid gives 45% of 4-acetoxy-o-xylene (Table I); this would appear to indicate that acetic acid can add to the initially formed carbonium ion. It is, however, not possible to exclude completely the possibility of the formation of acetic anhydride in this system, by sulphuric acid dehydration of acetic acid - and consequent formation of acetyl nitrate. The N.m.r. spectrum of a solution of sulphuric acid in acetic acid in the concentrations used showed no sign of acetic anhydride, even after 24 hours' standing; similarly, the N.m.r. spectrum of a solution of sulphuric acid/nitric acid in acetic acid showed no sign of acetic anhydride. However, in the presence of nitric acid, any acetic anhydride formed would be converted largely to acetyl nitrate, which is indistinguishable from acetic acid by N.m.r.[38]. Moreover, if acetic acid were an effective nucleophile in this reaction, acetoxy product would be expected from treatment of o-xylene with nitric acid in acetic acid; in fact this reaction has been studied[78,79] and no acetoxy products were reported.

The nitration of o-xylene by preformed acetyl nitrate (silver nitrate and acetyl chloride) in acetonitrile also gives large quantities (39%) of 4-acetoxy-o-xylene, and the product ratios obtained are almost identical with those obtained with nitric acid-acetic anhydride in acetonitrile

solution (Table I). Here, acetyl nitrate is almost certainly providing acetate for the second step, but it is impossible to rule out completely the presence of acetic acid, since acetyl chloride is readily hydrolyzed by atmospheric moisture, and acetic acid is a frequent trace impurity in acetonitrile.

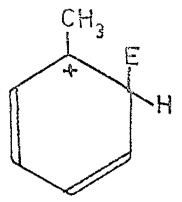
Some reactions with o-xylene were carried out in chloroform solution at -15°, by mixing equimolar amounts of nitric acid and acetic anhydride in chloroform at room temperature, cooling to -15° (which freezes the equilibrium which forms acetyl nitrate[11]) and adding this mixture to a solution of o-xylene, and acetic acid or acetic anhydride in chloroform at -15°. The results (Table XXVIII) show that as small amounts of acetic acid or acetic anhydride are added to the solution, the amount of acetoxy product rises sharply. Both these substances, therefore, under these conditions appear capable of taking part in the addition step.

These observations seem to show that acetyl nitrate, acetic acid, and acetic anhydride can all act as the nucleophile in the second step of the reaction. However, since in no case was only one of these reagents unequivocally present, other interpretations are possible.

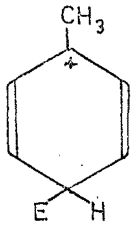
(5) Electrophilic attack at an alkylated position

Initial electrophilic attack on a ring carbon bearing

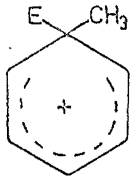
a methyl group is not unexpected, since in many cases these sites are just as activated towards electrophilic attack as are the hydrogen-bearing ring atoms. In o-xylene, for example, the 3- and 4-positions are activated by ortho and meta, and para and meta, methyl groups respectively, while the 1 and 2 (methylated) positions are activated by an ortho methyl group. For attack at a methylated position there will also be some activation by the methyl group at the reaction site. Methyl groups are activating and ortho-para directing in aromatic electrophilic substitution, and this is attributed[80] to the contribution to the σ-complex of structures XIV and XV. In these, the positive charge is located on a carbon atom next to a methyl group, which can stabilize this positive charge either by inductive or hyper-conjugative effects. Similar structures are not available for meta substitution;



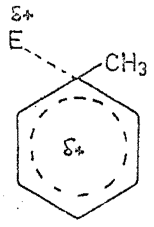
XIV



XV



XVI



XVII

nor are such structures available for the ion XVI, and little activation by the methyl group at the reaction site

might be expected. However, the transition state for nitration occurs earlier on the reaction coordinate than the σ-complex[80], so that the transition state resembles XVII. Such a transition state will be stabilized by the methyl group. This stabilization must be significant because 3% acetoxylation occurs with toluene when such a methyl group provides the only activation.

Similar attacks at alkylated positions presumably occur in other electrophilic substitution reactions of alkylbenzenes, but in the absence of a suitable nucleophile for further reaction, the carbonium ion formed can usually only decompose to starting materials. Thus only the products of attack at an unsubstituted site are normally observed. However, in suitable cases where other reaction paths are available to the σ-complex, products of attack at an alkylated position can be formed. Reactions like this include the dealkylation accompanying nitration and halogenation of polyalkylbenzenes[81,82], the isomerization of methylbenzenes in liquid HF[83], and the side-chain halogenation attending nuclear substitution during the halogenation of various polymethylbenzenes[84,85].

(6) Application of the mechanism to other alkylbenzenes

The mechanism outlined will explain most of the acetoxylation data for the series of methylbenzenes (Table

XXXIII), obtained by Wright[7] and this work. The mechanism requires for acetoxylation either an activated ring position bearing a methyl group *para* to the position of acetoxylation, or two methyl groups *para* to one another from which a diene can be formed that can give an acetate by a migration step. The 2- and 3- positions of toluene, the 3-position of *o*-xylene, and the 2- and 5- positions of *m*-xylene fulfil neither of these conditions, and thus no acetoxylation in these positions is observed. The methylated positions of toluene, *m*-xylene and mesitylene are deactivated relative to the free positions and thus very low proportions of acetoxylation relative to normal nitration are observed. The 2-position of hemimellitene is more activated for electrophilic attack (by two *ortho* methyl groups) than are the 1- and 3-positions (activated by one *ortho* and one *meta* methyl); accordingly, 35% 5-acetoxyhemimellitene is produced, from initial attack at the 2-position, and only 11% 4-acetoxyhemimellitene, from initial attack at the 1- and 3- positions. Similarly, in 3-bromo-*o*-xylene, the 2-position is more activated (*ortho* bromo, *ortho* methyl) than the 1-position (*ortho* methyl, *meta* bromo), and the major diene and corresponding acetate (those isolated) come from attack at the 2-position. (There was some evidence in the N.m.r. spectrum

Table XXXIII

Percentage acetoxylation of methylbenzenes with nitric acid/ acetic anhydride.

Hydrocarbon	Percentage Acetoxy Product
Toluene	3 (4-acetoxy)
o-Xylene	50 (4-acetoxy)
m-Xylene	1 (4-acetoxy)
p-Xylene	35
Hemimellitene	35 (5-acetoxy)
	11 (4-acetoxy)
Pseudocumene[a]	26 (5-acetoxy)
	10 (3-acetoxy)
Pseudocumene[b]	3
Mesitylene	0
Durene	31
Isodurene	5
Prehnitene[c]	54
Pentamethylbenzene	0
3-Bromo-o-xylene[d]	31

[a]G.J. Wright's figures

[b]Figures from present work

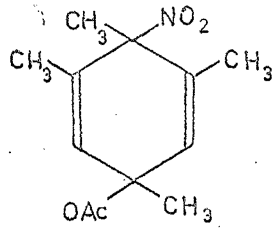
[c]Includes 11% acetoxy-nitroprehnitene

[d]Amount of diene present in reaction mixture.

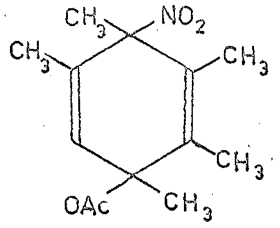
of the crude reaction mixture from 3-bromo-o-xylene of smaller amounts of the diene arising from attack at the 1-position but neither this nor the resulting acetate could be isolated.) As has already been mentioned, both acetoxy products reported by Wright from pseudocumene can be accounted for by acetate migration from a single diene intermediate formed by electrophilic attack at the 1-position, the most activated (ortho methyl, para methyl) of the methyl-bearing ring carbons. Durene and prehnitene both have methylated positions of approximately the same reactivity as the unsubstituted positions, and thus should form dienes, and hence acetoxy products as observed - durene gives 31% acetate, and prehnitene gives 43% acetate, together with 11% nitro-acetoxyprehnitene, which almost certainly comes from subsequent nitration of acetoxyprehnitene which is nitrated under the conditions of the reaction (whereas nitroprehnitene is not acetoxylated und conditions).

The small amount (5%) of acetoxy product fr and the total absence of acetoxy product from pe benzene are two results which are less readily u Both these compounds have methylated positions o reactivity to the free ring positions, and shoul to give the dienes XVIII and XIX respectively, f acetate migration would lead to acetoxy products

Nitration at a methylated position may be occurring in these compounds but leading to phenylnitromethanes; this point is discussed in the next section. There is also an unfavourable statistical factor in the case of isodurene. Only one of the methylated ring positions is as active as the free positions, whereas in durene and prehnitene all four methylated ring positions are activated and comparable in reactivity to the free ring sites.



XVIII



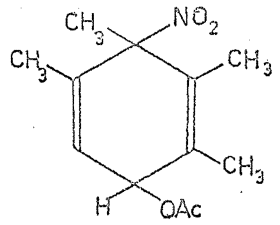
XIX

(7) Acetates for which dienes were not isolated

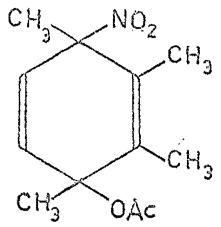
The foregoing discussion assumes that in all cases aryl acetates arise via a diene intermediate, although only for four substrates has this been shown, and the dienes isolated. Attempts were made to isolate dienes from other substrates which gave substantial amounts of acetoxy products - durene, prehnitene, and the diene corresponding to 4-acetoxyhemimellitene. The crude reaction mixtures at room temperature showed by N.m.r. the aromatic acetates, with no sign of the dienes. However, when the reaction of

of prehnitene was carried out at -40°, the N.m.r. spectrum at this temperature showed a series of peaks with complex coupling in the region δ = 5.54-6.25 ppm, and very little aromatic acetate was present. As the reaction mixture warmed up to -20°, these peaks disappeared and the aromatic acetate absorptions appeared. It is almost certain, therefore, that the acetoxylation of prehnitene takes place through a diene intermediate which is unstable and quickly breaks down under the normal conditions of the reaction. In view of this, and of the fact that in the cases where the dienes are relatively stable, N.m.r. analyses (Tables IV-VII) of the reaction mixtures showed that all the acetoxy products come from dienes, this assumption of acetoxylation via diene formation is a reasonable one.

Prehnitene could give two diene intermediates (XX and XXI), each of which could decompose to 5-acetoxyprehnitene. The complex coupling of the N.m.r. diene absorptions shows that at least some XX is present, since each isomer of XXI would be expected to give only a singlet in the diene region by analogy with the isomers of IV (p. 93) - since H^6 in I (p. 93) is uncoupled, the extra methyl group would not be expected to cause any splitting. Smaller amounts of XXI may be present.



XX



XXI

(8) Scope of the acetoxylation reaction

With this mechanism operating, acetoxylation in the nitric acid-acetic anhydride system will be a reaction of limited scope since it requires an activated, substituted position on the ring. Neither the addition-elimination sequence proposed by Ridd[8a], nor the electrophilic acetoxylation proposed by Fischer et al[2] could satisfactorily explain the complete absence of acetoxy products from anisole. In terms of the present mechanism, NO_2^+ attack will not occur at the methoxy-substituted ring position (which is not activated), and acetoxylation will not take place. When a methoxy-substituted position is sufficiently activated relative to the unsubstituted positions, however, nitration at this position followed by addition of an acetoxy group should be possible. Veratrole (1,2,3-trimethoxybenzene), in which the central methoxy-bearing carbon is activated by two other methoxy groups ortho to it, gives at least 3% and possibly up to 45% 5-acetoxyveratrole[38]. Since this compound is not the isomer expected from an electrophilic attack, it is likely that it, too, is formed by an addition-elimination mechanism.

Phenylnitromethane and Aldehyde products

Several substrates give rise to phenylnitromethanes and/or aldehydes on reaction with nitric acid-acetic anhydride. These results are summarized in Table XXXIV.

(1) Phenylnitromethanes

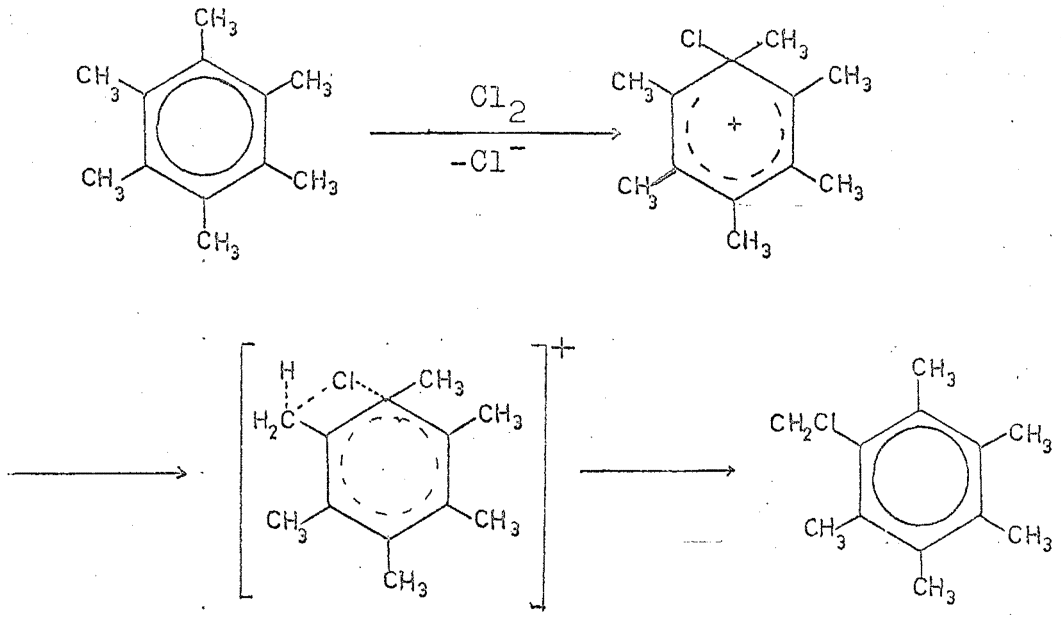
The formation of phenylnitromethanes is similar to the side-chain halogenation which accompanies nuclear substitution in the reactions of polymethylbenzenes with chlorine[84], bromine[86] or ICl[87] in acetic acid. Baciocchi and Illuminati have shown[84] that these side-chain reactions take place via an initial electrophilic attack on the ring, and not the free radical mechanism by which side-chain halogenation of less highly alkylated aromatics is effected[88]. Their study of the side-chain chlorination of a series of compounds C_6Me_5X (X = H, CH_3, CN, Cl) showed that kinetically the reaction was very similar to the ring chlorination of methyl-benzenes with activation parameters falling within the same range, that substituent effects on rates are very similar to those observed in aromatic substitution (and quite different from those observed in free radical reactions, which are much less selective), and that u.v. light had no influence on the rates. They propose[84,85] that this side-chain halogenation results from electrophilic attack at a methylated position to give an arenonium ion which cannot rearomatize by expulsion of a proton, and

Table XXXIV

Percentage phenylnitromethanes and aldehydes in the reactions of some aromatic substrates with HNO_3/Ac_2O

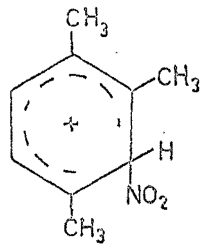
Substrate	% Phenylnitromethane	% Aldehyde
Pseudocumene	41	-
Isodurene	15	7
Durene	11	3
Prehnitene	21	-
Pentamethylbenzene	37	8
Hexamethylbenzene	25	-

which therefore rearranges to give the observed product. The limited extent of solvolysis during the reaction was considered evidence that the rearrangement step is intramolecular, and therefore the mechanism illustrated below for hexamethylbenzene was suggested.

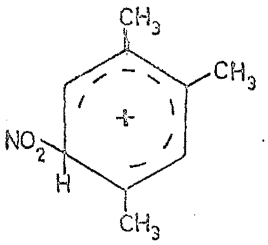


The similarity of the reaction conditions makes it probable that the side-chain nitration observed in the present work also arises from an initial electrophilic attack at a methyl-substituted ring position. It is, however, evident that the mechanism outlined above cannot account for the products formed, for it requires that the nitro group rearrange from one methyl-substituted position to another methyl group ortho to it. In two cases (pseudocumene and isodurene), the side-chain nitration

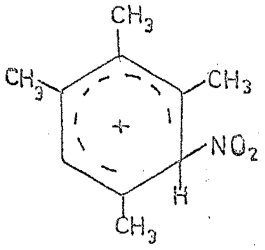
occurs on a methyl group which has only unsubstituted ring positions ortho to it. If the side-chain nitration is to occur by an intramolecular transfer of the nitro group, this necessitates that the rearrangement take place from the "normal" σ-complexes (XXII or XXIII, and XXIV) which lead to ring substitution. This is unlikely, since such ions can readily rearomatize by simple proton loss, and also because only one side-chain nitro product is formed from each compound; XXII and XXIV could each transfer the nitro group to two different methyl groups.



XXII

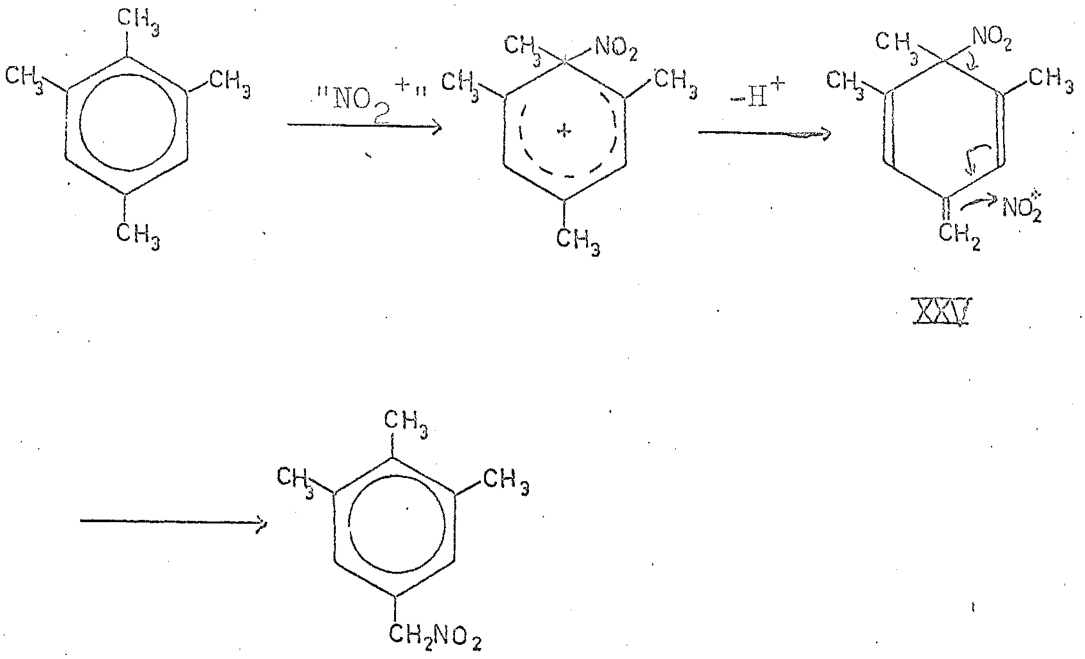


XXIII



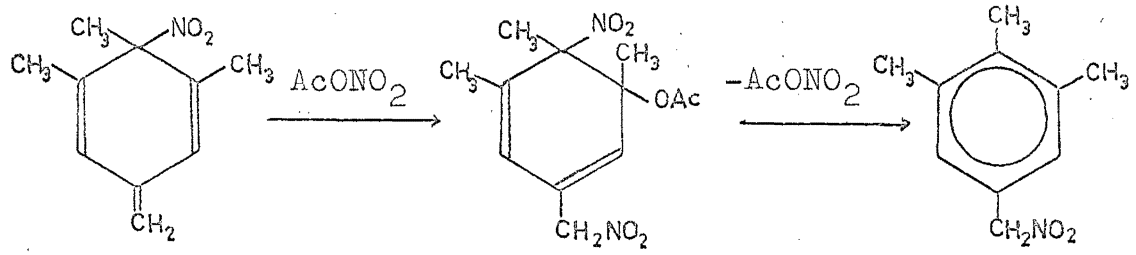
XXIV

It is noticeable that for all the hydrocarbons for which side-chain nitration is observed, the phenylnitromethane isomer formed is the one resulting from substitution on the methyl group para to the most activated, methyl-substituted ring position, and that, furthermore, none of the hydrocarbons which do not have a methyl group para to such a position afford the products of side-chain nitration. One mechanism which would account for this is:



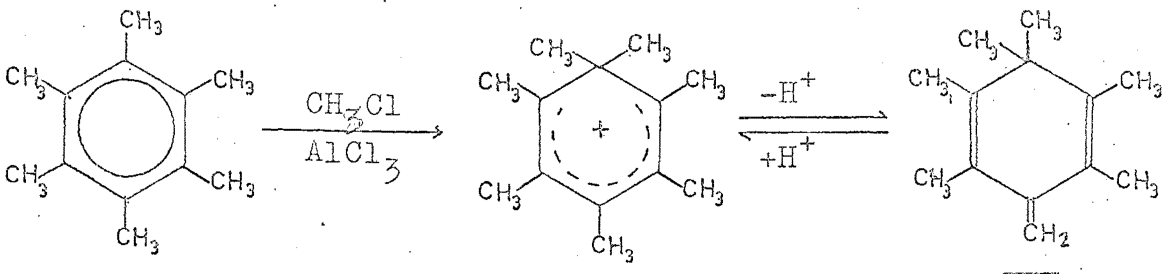
XXV

Alternatively, the conversion of XXV into the final product may take place by a second addition step, as proposed by Robinson[89] for the formation of 1-methyl-4-nitromethylnaphthalene from 1,4-dimethylnaphthalene and nitric acid-acetic anhydride.



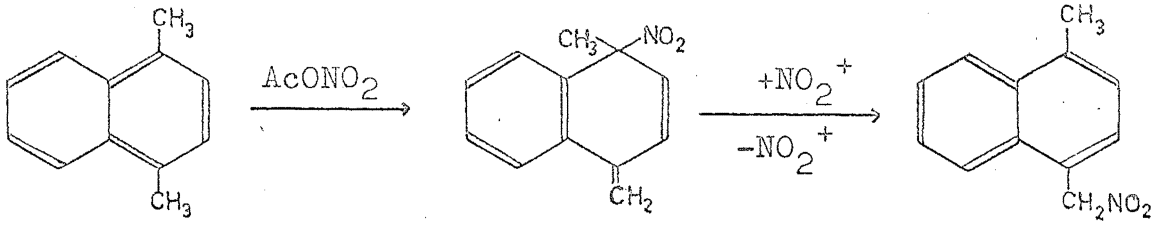
A methylenecyclohexadiene intermediate XXVI similar to XXV has been isolated[90] from the methylation of hexamethylbenzene, and a similar reaction sequence proposed

for its formation.



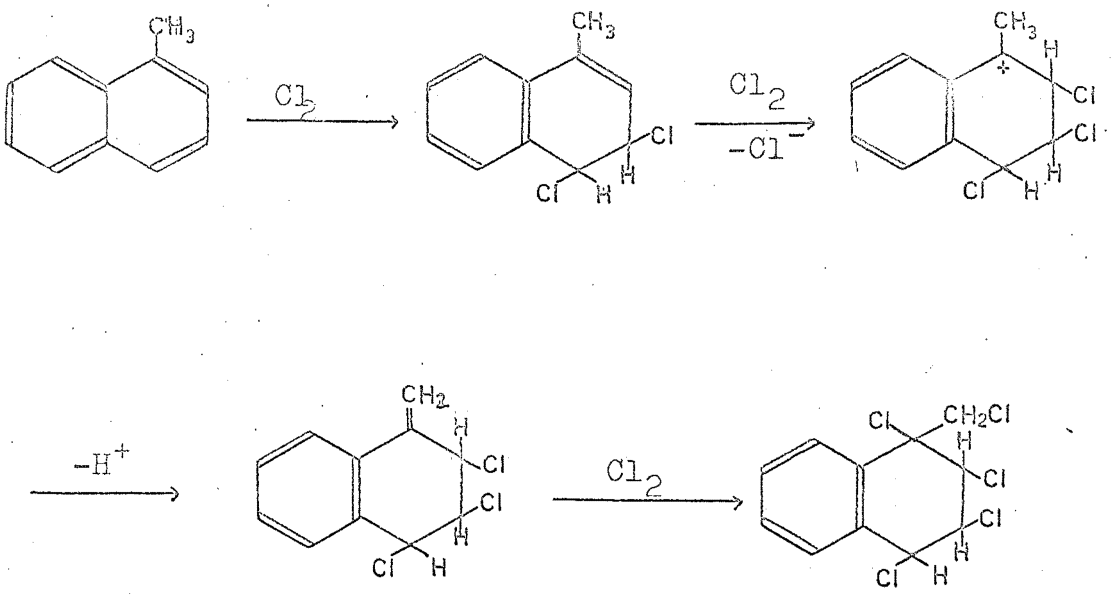
XXVI

A compound like this (XXVII) may also have been isolated[89] from the nitration of 1,4-dimethylnaphthalene; it too undergoes further reaction to a side-chain nitro product.

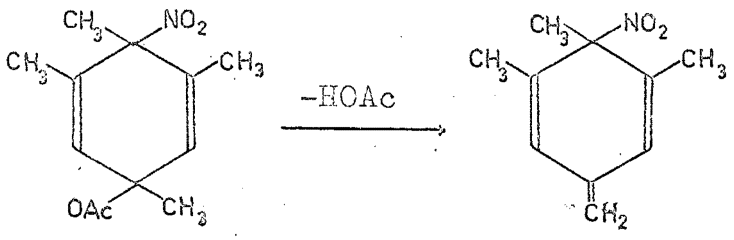


XXVII

A scheme of this type has also been proposed[91] to account for the side-chain chloro products found in the chlorination of 1-methylnaphthalene with $SOCl_2$.



Formation of the methylenecyclohexadiene intermediate XXV by decomposition of a diene intermediate must also be considered - the path proposed[89] for side-chain nitration of 1,4-dimethylnaphthalene. This is perhaps



not as likely as formation by proton loss from the σ-complex, because the diene of this type isolated from the nitration of p-xylene (IV) did not decompose in this manner. However, the marked differences in the relative importance of acetoxylation and side-chain nitration which occur even between

compounds which are apparently similar are difficult to explain on any grounds, so the lack of side-chain nitration of p-xylene cannot be considered as definitely ruling out this elimination of acetic acid from the diene.

(2) Aldehydes

Isodurene, durene and pentamethylbenzene form small amounts of aldehydes in the reaction with nitric acid-acetic anhydride (Table XXXIV). In each case the methyl group oxidised is the one at which α-nitro-substitution occurs, and no aldehydes are formed in reactions with no side-chain nitration. It is likely, therefore, that these aldehydes arise in much the same way as the phenylnitromethanes. Treatment of the phenylnitromethanes with nitric acid-acetic anhydride under the conditions of the reaction did not lead to formation of aldehyde. Presumably, therefore, the aldehydes arise from an alternative reaction of the methylenecyclohexadiene precursors to the phenylnitromethanes.

(3) Side-chain nitration versus acetoxylation

If the phenylnitromethane and aldehyde products are formed by the mechanism proposed, they are being formed competitively from the same carbonium ion which leads to acetoxylation, and possibly even from the same diene. This competition gives some explanation of the small amounts of aryl acetates observed from isodurene, pentamethylbenzene

and pseudocumene (this work), since these compounds give quite large amounts of aldehyde and side-chain nitro products. The fact that p-xylene has methyl groups suitably placed to give side-chain nitration, but none is observed, shows that more methyl groups are needed before side-chain nitration becomes competitive. This could reflect either an increase in the acidity of the hydrogens of the reacting methyl group, or a slower addition of acetate to the carbonium ion, perhaps because of increasing steric hindrance to addition when more methyl groups are present. In either case, the preferred reaction of the carbonium ion could become proton loss to give a methylenecyclohexadiene, and ultimately side-chain nitration, rather than addition of acetate to give a diene, and ultimately acetoxylation products. It is difficult to understand, however, why this sudden increase in the importance of side-chain nitration relative to acetoxylation should occur with isodurene and pentamethylbenzene, when a very similar system in durene gives substantially more acetoxy product than side-chain nitration.

A possible alternative explanation of the lack of acetate in the reaction with isodurene, pentamethylbenzene and pseudocumene is that the diene adducts are formed as usual, but decompose by different paths - either into starting material, as is observed to some extent with the

analogous dienes from p-xylene, or into the methylenecyclohexadiene which leads to side-chain nitration. These paths might be expected to become more significant for hydrocarbons with more methyl groups, when decomposition by acetate migration could be hindered, either sterically or by the reduced acidity of the ring protons. Once again, however, it is difficult to see why this should apply to isodurene, pentamethylbenzene and pseudocumene, but not to durene, which gives aryl acetate by a migration step.

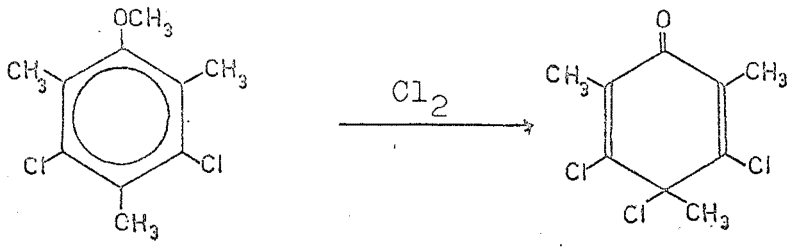
There is a clear conflict between the results obtained in the present work, and those obtained by Wright[7] in earlier work, for the nitration of pseudocumene with nitric acid-acetic anhydride (Table XXXIII). In an endeavour to reproduce Wright's results many adjustments to the conditions of the reaction were made. The reaction was run using freshly distilled nitric acid, undistilled nitric acid, urea (2%) in nitric acid (to remove nitrous acid), acetic anhydride distilled off sodium (Wright's acetic anhydride was purified in this manner), acetic acid solvent, sodium acetate added to the reaction, and pseudocumene dried and redistilled after the method of Wright. In all cases the same product distribution (with little aryl acetate, and about 40% phenylnitromethane) was obtained, to within a few per cent. While this gross change in product distribution has not been explained, it does lend credence to the

hypothesis that both the phenylnitromethanes and the aryl acetates arise from a common intermediate, which has been diverted one way under Wright's conditions, and another way under slightly different conditions. Since every effort was made to get the conditions exactly the same, it also shows that very little is needed to swing the reaction away from aryl acetate products, and towards side-chain nitration, and vice versa. In view of this delicate balance it is perhaps not surprising that some substrates give largely products of side-chain nitration, while others, apparently structurally similar, give products of acetoxylation.

(4) Side-chain substitution in earlier work

The mechanism proposed for side-chain nitration (via a 4-methylenecyclohexa-2,5-diene) can also be used to explain the results of Baciocchi and Illuminati[84,85] (p. 125), since the evidence upon which these workers have based their proposed mechanism is rather slim. In no case did these workers identify which of the possible isomers of the side-chain chlorinated products were present ; thus their evidence that a methyl group ortho to the point of electrophilic attack is necessary for reaction to occur rests on the failure to observe side-chain chlorination with 1,3,5-tri-t-butylbenzene, and on the special course of the reaction with 2,4,6-trimethyl-3,5-dichloroanisole (XXVIII) in which side-chain chlorination is likewise not found.

Since both these compounds lack a methyl group para to the point of electrophilic attack, these observations are equally compatible with side-chain chlorination via a para



XXVIII

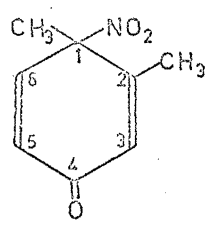
methylene compound. Their evidence for intramolecular transfer of chlorine rests largely on the limited extent of solvolysis during the reaction; however, the reaction with ICl[87] to give nuclear substituted iodo products but side-chain substituted chloro products is evidence against an intramolecular rearrangement.

Cyclohexadienone Intermediates

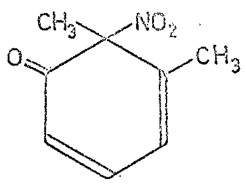
The reactions of 4-bromo- and 4-acetoxy-o-xylenes with nitric acid-acetic anhydride gave an unexpected product, 6-nitro-3,4-xylenol. This was found to be produced via a cyclohexadienone intermediate. This intermediate, and its formation and decomposition are discussed in this section.

(1) Structure of the dienones

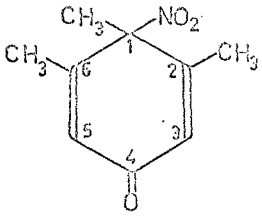
The cyclohexadienone structure for the precursor of the nitro-phenol from 4-bromo- and 4-acetoxy-o-xylene is established by the mass spectral molecular weight and fragmentation pattern (which is clearly distinguishable from those of the nitrophenols), the positions of the ring protons (6.25 - 6.90 ppm) and the methyl protons (1.90-2.05 ppm) in the N.m.r. spectrum (outside the ranges of absorption in aromatic molecules[66]), and the presence of nitro and carbonyl absorptions in the I.R. spectrum. On the basis of the behaviour of the other substrates studied, which give only 1,4 addition, the 2,5-dienone structure XXIX is expected rather than a 2,4-dienone structure like XXX. The spectral data also favour XXIX. The N.m.r. chemical shifts and coupling constants are consistent with those observed in other cyclohexa-2,5-dienones[92], and, while N.m.r. data on cyclohexa-2,4-dienones are sparse, it appears[31] that hydrogens α to the carbonyl in these compounds absorb further upfield



XXIX



XXX



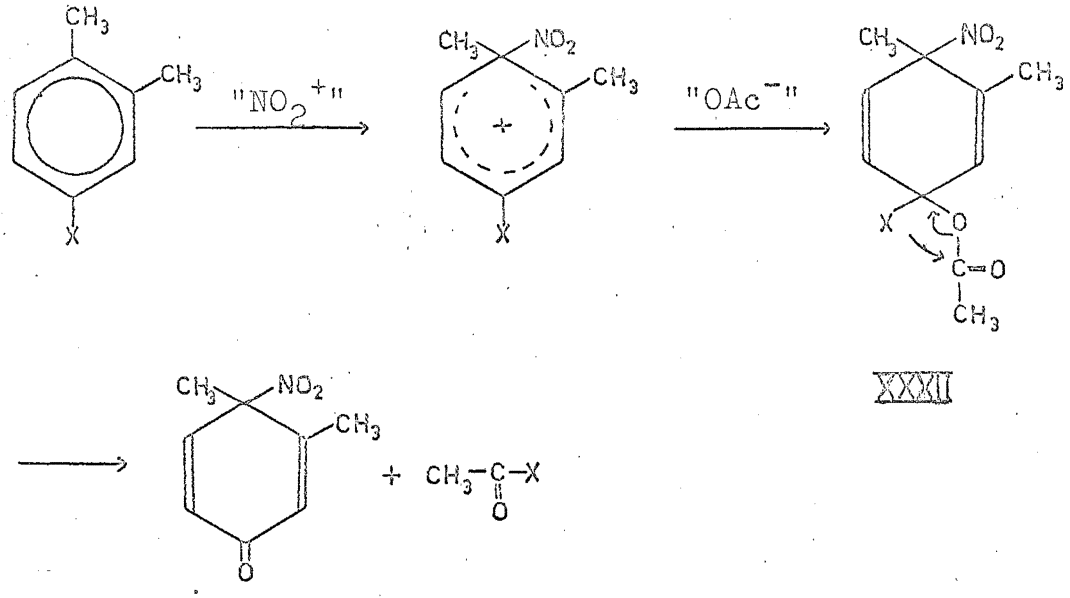
XXXI

than any absorptions in the dienone isolated. The three carbonyl absorptions (1670, 1630, 1610 cm^{-1}) in the I.R. spectrum are characteristic of a cyclohexa-2,5-dienone structure[31]; the third of these has only in a few cases been reported for cyclohexa-2,4-dienones, and then at lower frequencies (1560-1570 cm^{-1}). The u.v. (λ_{max} 224 nm) also indicates a cyclohexa-2,5-dienone. This is slightly lower than that normally observed for these systems (230-265 nm) but electron-attracting substituents are known to cause a shift to lower wavelengths[31]. Cyclohexa-2,4-dienones absorb at much higher wavelengths (290-340 nm)[31].

The structure XXIX is therefore assigned to this dienone. Since this work was completed, A.J. Lewis has isolated[93] a similar dienone in the nitration of 5-bromo-, 5-acetoxy- and 5-methoxyhemimellitenes, assigned the corresponding structure XXXI. The simplicity of the N.m.r. spectrum in this case (C^2H_3, C^6H_3 coincident, and H^3 and H^5 coincident), which is expected from the symmetry of the molecule, is confirmatory evidence of the structure.

(2) Mechanism of formation of dienones

The structure of the dienones makes it likely that their formation is simply a special case of the 1,4 addition leading to the dienes. When, as in the cases of 4-bromo and 4-acetoxy-o-xylene, the diene (XXXII) has a good electronegative leaving group attached to C^4, it is unstable and elimination occurs to give the dienone. The mechanism proposed is therefore



XXXII

Lewis[93] has extended the reaction to 4-methoxy-o-xylene, and to 5-substituted hemimellitene derivatives. Dienones are formed in all cases. His results, together with those for 4-bromo- and 4-acetoxy-o-xylenes are collected in Table XXXV. In each case, the substrate with the methoxy substitutent gives considerably less dienone

Table XXXV

Products from substituted o-xylenes and hemimellitenes with nitric acid-acetic anhydride.

	4-X-o-xylene			5-X-hemimellitene	
X	Dienone	$5\text{-}NO_2\text{-}4\text{-}X$-oxylene	other[a]	Dienone	$4\text{-}NO_2\text{-}5\text{-}X$-hemimellitene
Br	46	45	9	60	40
OAc	67	25	8	73	27
OMe	12	64	24	23	77

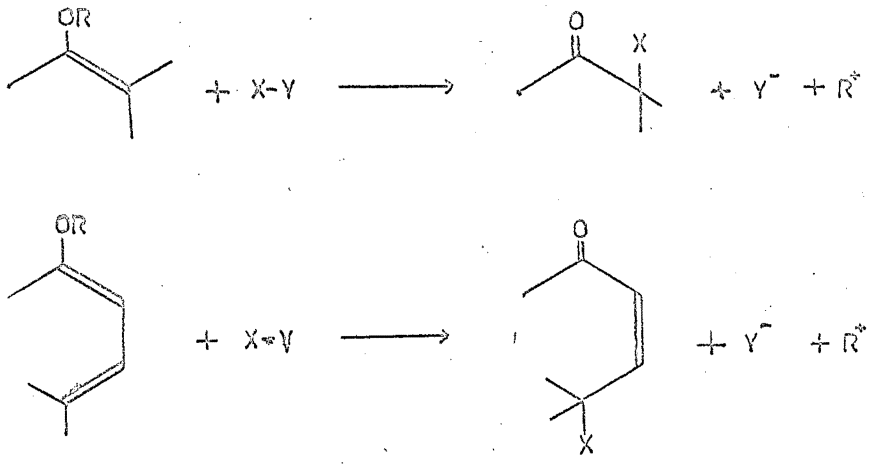
[a]Other isomers of nitro-4-X-o-xylene

than those with other substituents. This is not unexpected, since alkoxy groups are known[94] to be poorer leaving groups than bromo or acetate groups in most nucleophilic substitution reactions.

The proposed mechanism requires the intervention of a diene intermediate (XXXII), and detection of such an intermediate would provide confirmation of the mechanism. No such evidence could be found on examination of the

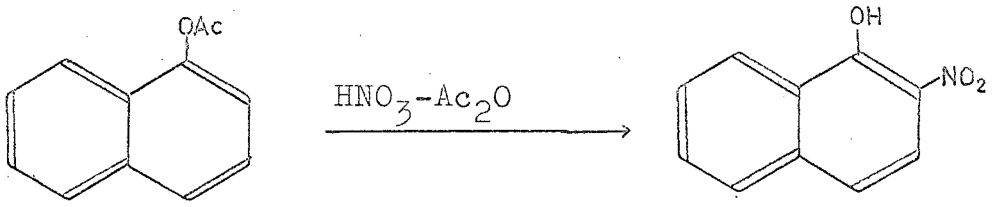
reactions of 4-bromo- and 4-acetoxy-o-xylene, even immediately after mixing the reagents. In the case of 5-methoxyhemimellitene, where the methoxy group is a relatively poor leaving group and the diene might be expected to be more stable, Lewis found that the N.m.r. spectrum of the reaction mixture showed absorptions in the diene region which did not correspond to the isolated dienone, nor to any other isolated product. These may have been due to the diene precursor of the dienone, but Lewis was not able to obtain more detailed information.

This type of electrophilic addition with rearrangement is well-known in simple olefins, both 1,2 addition[95] and 1,4 addition[96] having been observed.

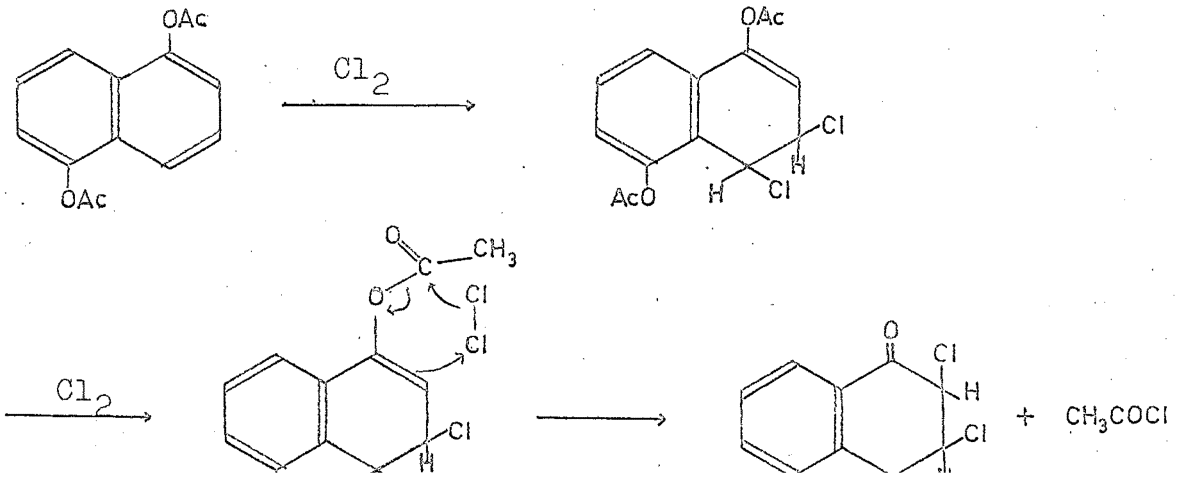


In aromatic substitution, it is a well-known reaction of phenols (R = H; p.16), and is an uncommon but not unprecedented reaction of alkoxy and acetoxy substituted compounds[97] (R = alkyl, acyl), though it has not apparently

been observed before for halogeno substituents. Again, both 1,2 addition[97] and 1,4 addition[32] are known. As well as those cases in which the dienones have been isolated, there are[97] other instances in the literature where the nature of the products makes it probable that such intermediates are involved; the formation[98] of 2-nitro-1-naphthol as the major product in the nitration of 1-naphthyl acetate is a case in point.



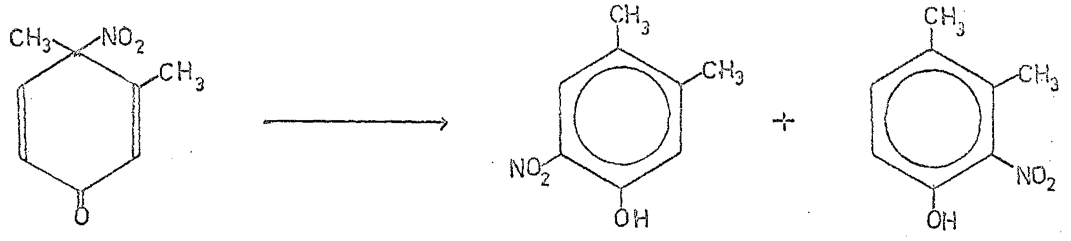
For 1,2 additions such as this it is possible[97] that a cyclic transition state is involved rather than a true intermediate like XXXII. Thus the formation of the keto adduct during the chlorination of 1,5-diacetoxynaphthalene may proceed as follows[97]



This is unlikely for the 1,4 additions observed in the present work, and impossible in the case of the bromo-substituent. Here, there is no oxygenated species initially attached to the ring to allow such a mechanism to occur; the oxygen which forms the carbonyl group must come from a preliminary addition to the ring by acetate.

(3) Decomposition of dienones

The decomposition of the dienone from 4-X-o-xylene in a number of solvents follows the path below, with a 1,3 migration of the nitro group to give two isomers of nitro-3,4-xylenol.

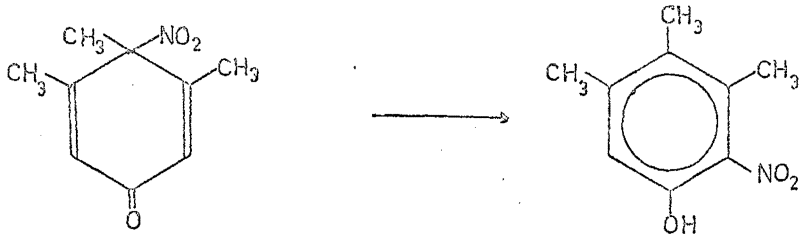


HOAc, $CHCl_3$, DMSO:	65%	35%
Aqueous acetic acid:	85%	<5%

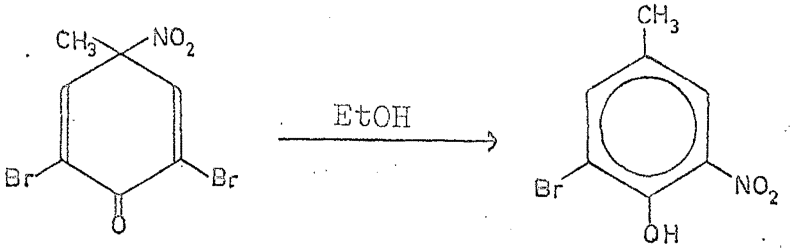
Mass spectral analysis of the products showed that dinitro-3,4-xylenol was also present; there could only have been small quantities (<5%) of this since it was not evident in the N.m.r. spectrum of the decomposition products.

Lewis has found[93] that the dienone from 5-X-hemimellitene decomposes by a similar 1,3 nitro migration; in this

case only one product is possible.

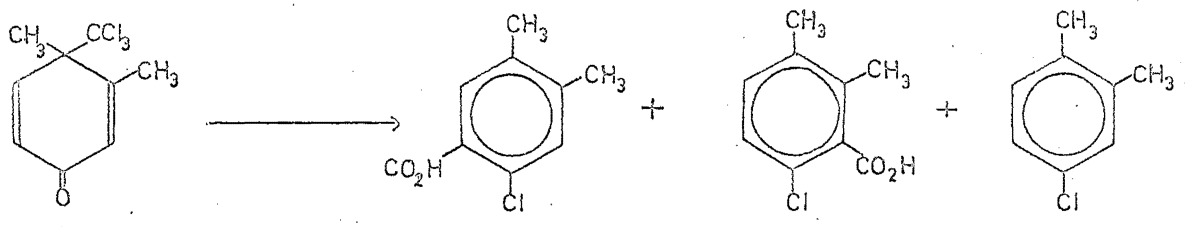


Such an aromatization by a 1,3 migration is unusual for a cyclohexa-2,5-dienone, but not unprecedented. Very few 4-nitro-cyclohexa-2,5-dienones are known, and in most of them this type of migration is blocked by alkyl groups in the 2 and 6 positions; aromatization therefore takes place by loss of either the nitro group or the other group in the 4-position[99]. However, some instances are known of 4-nitrocyclohexa-2,5-dienones with halogens in the 2 and 6 positions in which 1,3 nitro migration occurs, with expulsion of the halogen atom[100]. The reaction below is an example[100d,e].

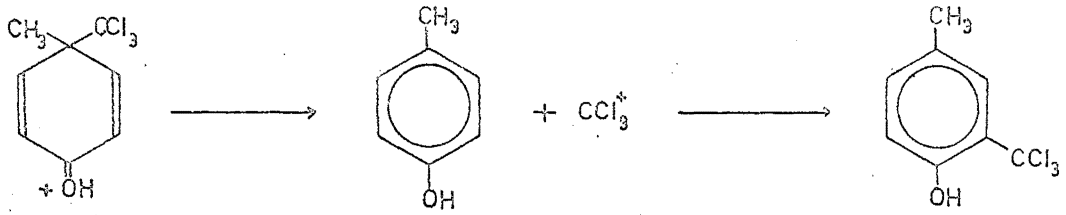


There are more instances of 1,3 migration during aromatization with 4-halomethylcyclohexa-2,5-dienones[31], though

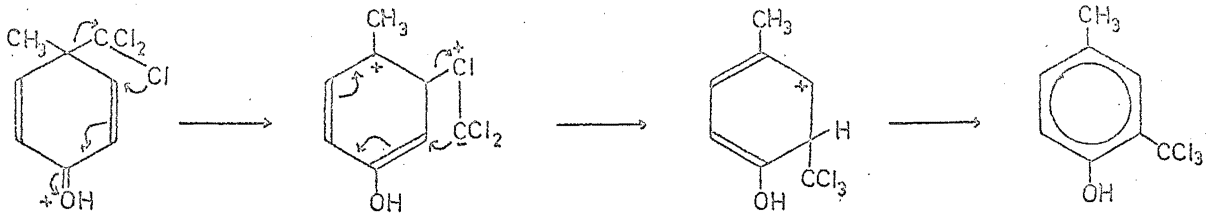
these are likely to be attended by other reactions like hydrolysis of the halomethyl group. The products of the reaction of 4-trichloromethyl-3,4-dimethylcyclohexa-2,5-dienone with polyphosphoric acid[101] are shown below.



There is, however, very little information on the mechanism of this rearrangement, and several sequences have been proposed. Miller suggests[102] that the migration of the $-CCl_3$ group takes place by liberation of a CCl_3^+ cation which then attacks the phenol (Scheme A), or alternatively that two intramolecular steps occur (Scheme B).



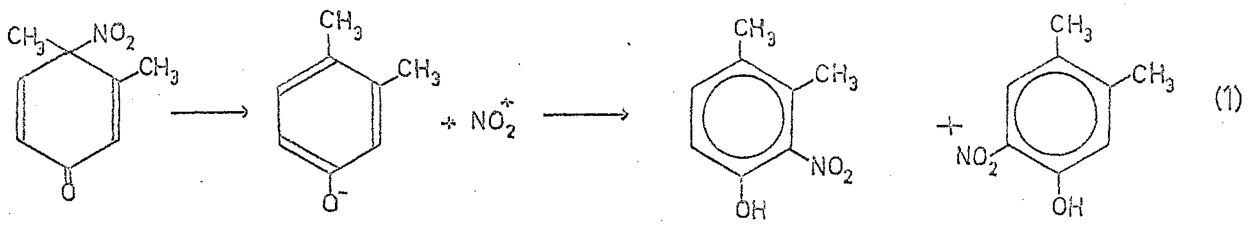
Scheme A



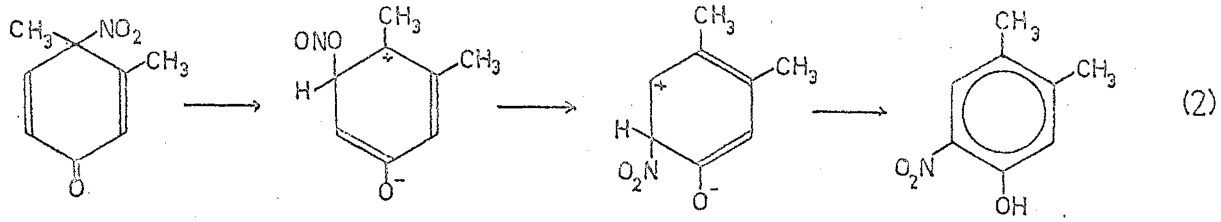
Scheme B

An alternative proposal[31,100e] is that the migrating group separates as a free radical (CCl_3. or .NO_2) and that the radicals recombine to give the observed products.

Each of these mechanisms is available for the migration process observed in the present work; in addition there is the possibility that the nitro group separates as an anion before recombination. Possible mechanisms are set out below, and the available evidence does not permit an unequivocal decision amongst them.

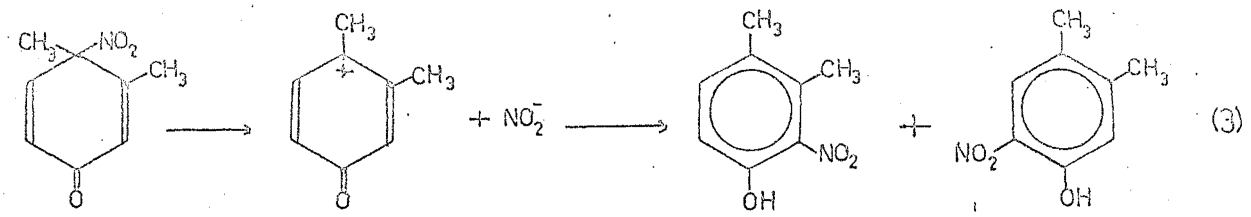


(1)

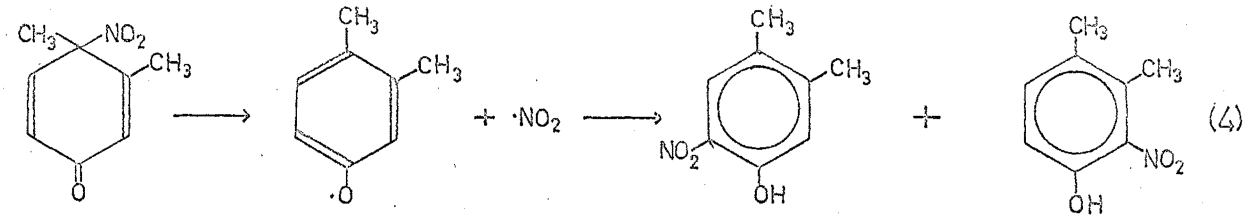


(2)

(+ isomer) (+ isomer) (+ isomer)



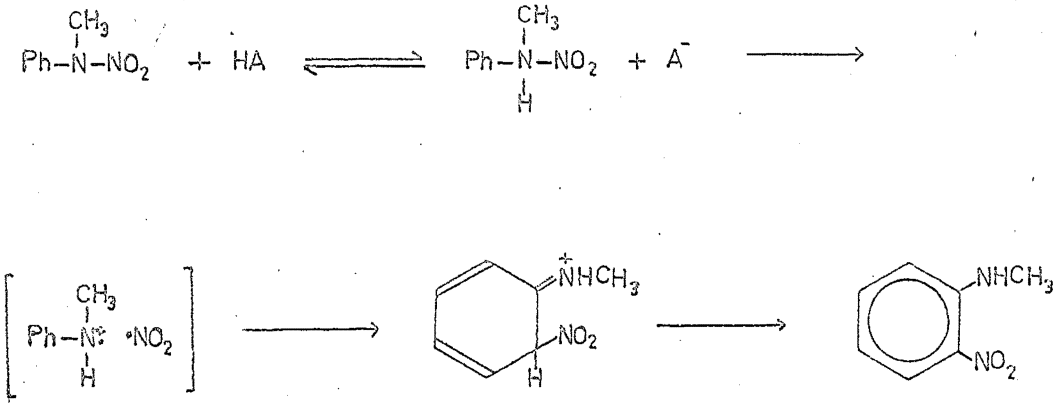
(3)



(4)

Decomposition of the dienone from 4-bromo-o-xylene in acetic acid or DMSO in the presence of bromide or acetate ions in equimolar quantities produced no incorporation of these anions into the product; incorporation would be expected if the nitro group were released as a free anion which made a subsequent attack on the cationic species. Similarly, decomposition in the presence of equimolar quantities of 3,5-xylenol gave no nitro-3,5-xylenol which would be an expected product if free NO_2^+ were released. These results may, of course, simply mean that no completely free ions are released, but that instead ion pairs are formed which recombine to give the phenolic products. However, the presence of small amounts of dinitrophenols in the decomposition argues that at least part of the reaction is

intermolecular. Furthermore, Lewis has found[93] that decomposition of 4-nitro-3,4-dimethylcyclohexa-2,5-dienone in acetic acid in the presence of $N^{15}O_2^-$ incorporates N^{15} into the nitrophenols in 83% of the amount expected if all NO_2^- in the system were pooled. This indicates that most, if not all, of the reaction is intermolecular. These data are most consistent with a free radical mechanism, for the reaction of acid with $N^{15}O_2^-$ would produce $N^{15}O_2$, and no incorporation of added anions or nitration of added aromatics would be expected. Such a mechanism would be very similar to that recently proposed[103] for the nitramine rearrangement:



The change in product ratios when decomposition of the dienone is carried out in aqueous solution may imply a change in mechanism. Lewis found that in aqueous acetic

acid decomposition was accompanied by little or no incorporation of N^{15} from $N^{15}O_2^-$. It would not be surprising if aqueous solution favoured an ionic mechanism, in contrast to a radical mechanism in less polar solvents.

The picture is, however, complicated by the fact that decomposition in acetic acid in the presence of $N^{15}O_3^-$ also resulted in 80% incorporation of N^{15} into the nitrophenols. This is relatively easy to explain in terms of a mechanism involving NO_2^+; the equilibrium between NO_2^+, NO_3^- and N_2O_5 could result in the formation of $N^{15}O_2^+$. Such an exchange between NO_2 and $N^{15}O_3^-$ is harder to envisage.

$$NO_2^+ + N^{15}O_3^- \rightleftharpoons \begin{matrix} O \\ \diagdown \\ N-O-N^{15} \\ \diagup \\ O \end{matrix}\!\!\begin{matrix} \diagup O \\ \diagdown O \end{matrix} \rightleftharpoons NO_3^- + N^{15}O_2^+$$

Other Products from Nitration of Hydrocarbons

The formation of phenylnitromethanes, aldehydes, aryl acetates and nitrophenols has been discussed. All these, together with the ring nitrated products can be accounted for in terms of initial nitration of the ring. Three products remain which have not been accounted for; these are the p-methylbenzyl acetate from p-xylene, 2,4,5-trimethylbenzyl alcohol from durene, and pentamethylbenzyl acetate from hexamethylbenzene. Small amounts of side-chain acetoxylation have been reported[84,87] accompanying side-chain halogenation of polymethylbenzenes in acetic acid; these have been attributed to solvolysis. This can scarcely be the case here, since it is hardly likely that such extensive solvolysis would occur for these three hydrocarbons and in no others, when side-chain nitration is a general reaction.

The side-chain acetoxylation of p-xylene is not a free radical reaction. The yield of p-methylbenzyl acetate is unaffected by running the reaction in the dark, under u.v. irradiation, or by using p-xylene which had been purified by distilling off sodium in an effort to remove possible impurities which may have been acting as free radical initiators.

The production of 2,4,5-trimethylbenzyl alcohol from durene is strongly dependent on nitrous acid concentration (Tables II and III); the relative yield in HOAc falls from 20% with old nitric acid (which showed a strong nitrite test) to 6% with carefully purified nitric acid, and is also reduced by the presence of urea. Complete removal of nitrous acid is not possible in this system, since the formation of aryl acetate by in situ diene decomposition releases nitrite. The formation of these compounds may well be unrelated to the general nitration reaction, since they appear only in these isolated cases. It is, perhaps, noteworthy that because of solubility problems the reactions of durene and hexamethylbenzene were run in much more dilute solutions than normal.

The Nature of the Nitration Reaction

(1) Kinetics of nitration with nitric acid-acetic anhydride

As indicated in the introduction, the nature of the nitrating species in nitric acid-acetic anhydride is not known with certainty. An attempt was made to study this problem by observing the kinetics of nitration of mesitylene and m-xylene with nitric acid-acetic anhydride in acetic acid solution by u.v. spectroscopy. These kinetics, together with those of other hydrocarbons, were also studied by the competition method, nitrating pairs of hydrocarbons and measuring relative reactivities. The results of this work, and the calculated relative rates (calculated from the benzene:toluene rate ratio together with reported[7] isomer ratios) are given in Table XXXVI.

Accuracy of results

There were initial problems due to variation in rates of reactions performed with batches of nitric acid distilled at different times. These were never really solved. Even when extreme care was taken during the distillation of the nitric acid (to avoid splashing, and to avoid warming the mixture during distillation which leads to the formation of nitrous species), the rate constant for mesitylene obtained by the u.v. spectrophotometric method varied

Table XXXVI

Relative reactivities of hydrocarbons in $HNO_3/Ac_2O/HOAc$

Hydrocarbon	From kinetic expts[a]	From competition expts[b]	Calculated
Mesitylene	1910	1950	75,000
m-Xylene	330	330	1,465
o-Xylene[c]		203	195
Toluene		29	29
Benzene		1	1

[a]Relative to m-xylene = 330 [b]Relative to benzene = 1

[c]Both observed and calculated figures include the acetoxylation reaction

by a factor of 2-3. The problem did not seem to be related to nitrous acid catalysis, since kinetic runs with nitric acid which had been kept for several days at room temperature, and which consequently had a relatively high nitrous acid content (between 5 and 10 times as much as fresh acid, according to the modified Gries-Ilosvay test[104]) showed no greater variation in the rate constant. However, the relative rates of reaction of mesitylene and m-xylene were found to be the same with each of three batches of nitric acid which showed this variation in the absolute rate constants. These results are summarized in Table XXXVII.

No further investigation of the problem was therefore made. Kinetic plots, and the relative reactivities from competition experiments were all obtained from the same batch of nitric acid, and should thus reflect only differences in substrate reactivity.

The rate constant for the nitration of m-xylene was calculated from a value of 8.26×10^2 for the extinction coefficient for the mixture of 2- and 4-nitro-m-xylenes. This figure assumes that the product contains 15% 2-nitro-m-xylene and 85% 4-nitro-m-xylene. These are the values obtained by Wright[7] for the isomer distribution in this reaction, and g.l.c. analysis of the completed reactions in the present work also gave these proportions. However, it can be calculated from the extinction coefficients at

Table XXXVII

Rate constants for nitration of mesitylene and m-xylene with different batches of HNO_3.

Batch No.	$k \times 10^3 (min^{-1})$ (mesitylene)	$k \times 10^3 (min^{-1})$ (m-xylene)	$[HNO_3]$
1	3.21	.545	.1938
2	2.46	.410	.1921
3	6.78	1.15	.1911
4[a]	5.90	.971	.1934

[a]Containing a high proportion of nitrous acid.

335 nm of the two pure nitro-m-xylenes (9.13×10^2 for 4-nitro-m-xylene, 3.37×10^2 for 2-nitro-m-xylene) that even if the proportions alter to the extent of giving 80% 4-nitro and 20% 2-nitro-m-xylene, or 90% 4-nitro- and 10% 2-nitro-m-xylene, the error in using the value 8.26×10^2 is only 3.5%. In fact, component ratios determined by g.l.c. do not vary by nearly this amount[7].

Tables XIX to XXIII show the reproducibility of the results obtained. Reproducibility is worst for the competitive nitration of benzene and toluene, where the difference in reactivity is greatest - the reaction therefore produces a relatively small amount of nitrobenzene, and any errors in analysis are proportionately magnified. Since the calculated relative reactivities of the other hydrocarbons are based upon this toluene:benzene rate ratio, there is a corresponding error in these calculated values, but in view of the very large differences between the calculated and observed reactivities of the more highly activated substrates, higher accuracy is not required.

Order of the reaction

In order to compare the reactivities of two substrates nitrated separately, the reaction must be first order in aromatic. Read[6,52] nitrated o-xylene and m-xylene in nitric acid-acetic anhydride and found a zeroth order dependence

on aromatic. Under the same conditions, it was found in this work that the reaction of mesitylene was also zeroth order. Addition of acetic acid to the mixture raised the order of the reaction with respect to mesitylene; presumably the acetic acid competes with the aromatic substrate for the reactive species, and slows this step down until it becomes rate-determining. Under the reaction conditions finally used, the reaction of mesitylene was found to be first order in aromatic, as judged by the initial slopes of rate plots of reactions with various concentrations of aromatic (Table XVII), and by the fit of the data to the first order rate law (Graph IV).

Although the first order rate plot for mesitylene under these conditions gives a good straight line over 75% reaction, the corresponding first order plot for m-xylene begins to tail off. This is probably because the side reaction between nitric acid and acetic anhydride[105] to give tetranitromethane becomes significant for the slower reaction of m-xylene.

$$4HNO_3 + 4(CH_3CO)_2O \rightarrow C(NO_2)_4 + 7CH_3CO_2H + CO_2$$

The rate of this reaction is not well-defined[52], but the work of Cohen and Wibaut[106] indicates that a 0.7 M solution of nitric acid in acetic anhydride begins to decompose quite rapidly after 200 minutes, with a half-life

for nitric acid of about 24 hours. The reagent used in the present work was a more dilute solution of nitric acid and acetic anhydride in acetic acid, and decomposition may well take longer. However, the time required for 75% nitration of m-xylene is 8-9 hours, and it seems likely that this side reaction will be significant over this period. The initial slopes of rate plots of reactions with various concentrations of m-xylene indicated the reaction to be first order in aromatic (Table XVIII).

Limiting rates in nitration

The results (Table XXXVI) show quite clearly that the more reactive hydrocarbons are in fact many times less reactive than they are calculated to be. This limiting of the maximum rate of nitration was also observed by Schofield and his co-workers[49] with nitric acid in various other solvents, as has already been discussed (p.24). Some of Schofield's results for nitration in sulpholan and nitromethane are summarized in Table XXXVIII. These results were interpreted in terms of encounter control of the reaction rate with sufficiently activated substrates, with the mechanism:

$$HNO_3 + H^+ \underset{k_1}{\overset{k_2}{\rightleftharpoons}} NO_2^+ + H_2O$$

$$NO_2^+ + ArH \underset{k_3}{\overset{k_4}{\rightleftharpoons}} \text{e.p.}$$

$$\text{e.p.} \xrightarrow{k_5} \text{products.}$$

Table XXXVIII

Nitration by HNO_3 in sulpholan and nitromethane

Substrate	Rel. rate (sulpholan)	Rel. rate (nitromethane)	Calc. rate (sulpholan)	Calc. rate (nitromethane)
Benzene	1	1	1	1
Toluene	20	25	20	25
o-Xylene	61	139	100	152
m-Xylene	100	146	1000	2350
p-Xylene	114	130	80	90
Mesitylene	350	400	48000	60000
Phenol	700		60000	

(e.p. = "encounter pair"). This leads to an expression for the observed first order rate constant $k_1(obs)$:

$$k_1(obs) = [NO_2^+] \frac{k_3 k_5}{k_4 + k_5}$$

For sufficiently reactive substrates (k_5 large), this reduces to

$$k_1(obs) = [NO_2^+] k_3$$

In such a case, therefore, the rate is determined solely by the concentration of nitronium ions, and by k_3, which in turn is governed largely by the viscosity of the medium. A limiting value of the rate of nitration is thus reached, beyond which an increase in substrate reactivity cannot produce a corresponding increase in reaction rate.

The limiting rate observed in the present work can also be accounted for in terms of such a scheme. If the nitronium ion were the reactive nitrating species, in light of Schofield's results, then, encounter control would be expected with nitric acid-acetic anhydride in acetic acid, since the viscosities of the media used are much the same (acetic acid 1.04, nitromethane 1.1). This is in fact the case; encounter control takes over at a level of reactivity somewhere between o-xylene and m-xylene both in the system used in this work, and in the organic solvents used by

Schofield. Such encounter control is, however, also compatible with nitration by protonated acetyl nitrate, since it requires only that the nitrating entity be present in sufficiently low concentration for k_3 to be comparable to or smaller than k_5. Any such reactive species could take the place of NO_2^+ in the second step of Schofield's reaction scheme, and in nitric acid-acetic anhydride one of the protonated acetyl nitrates may do so.

It seems likely, however, that the formation of any of the forms of protonated acetyl nitrate should be easier than the formation of NO_2^+; Dewar[51] has calculated this to be so. If this is the case, the concentration of protonated acetyl nitrate will be higher than that of NO_2^+. Encounter control with protonated acetyl nitrate as the nitrating agent should thus take over only at higher substrate reactivities than those observed, if at all. The fact that, in media of similar viscosity (nitromethane and acetic acid-acetic anhydride), encounter control sets in at very similar levels of reactivity, suggests that in both cases the nitrating agent is the same, NO_2^+. As Schofield has pointed out[49], however, extrapolation from one medium to another may not be possible; the factors affecting k_4 are not simple.

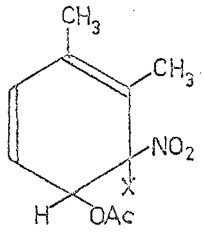
If encounter control takes over, as the results suggest, before the level of reactivity of m-xylene is

reached, all substrates of higher reactivity than m-xylene should react at the same rate. In fact mesitylene reacts six times as fast as m-xylene. It is a matter of conjecture whether this difference is significant. Schofield's results show a similar, though not as marked, change (mesitylene three times as reactive as m-xylene) which he does not regard as significant. However, in the present work, it is possible that the increase in rate with mesitylene reflects the beginning of the intrusion of a second mode of nitration via a less reactive but perhaps more plentiful nitrating agent, available only for more reactive substrates. Many nitrating species (NO_2^+, three possible protonated acetyl nitrates, acetyl nitrate) are present in nitric acid-acetic anhydride mixtures, so this possibility is a strong one. The very high relative reactivities observed by Dewar[50] (p.26) may be due to this, rather than to nitration through nitrosation.

(2) Nitration of deuterated o-xylenes

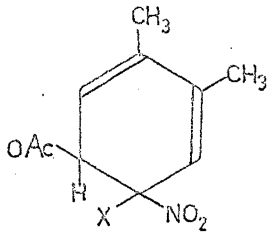
Since the σ-complexes leading to normal ring nitration products can readily aromatize by proton loss it is probable that no addition reaction involving these species occurs. It is still, however, possible that such addition occurs, to give, in the case of o-xylene, diene intermediates like XXXIII and XXXIV. Decomposition of these

species would have to be almost entirely by loss of HOAc to nitro products rather than by loss of HNO_2, since all the acetoxy product can be accounted for in terms of the isolated diene intermediate isomers.



XXXIII X = H

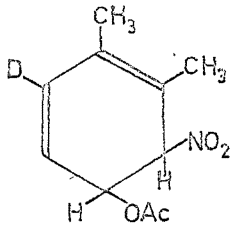
XXXV X = D



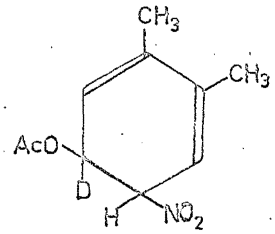
XXXIV X = H

XXXVI X = D

If the reactions were carried out with 3- or 4-deutero-o-xylene, the corresponding intermediates would be XXXV and XXXVI. Since only one of the 3-positions or one of the 4-positions is deuterated in these compounds, intermediates XXXVII and XXXVIII would also be present.



XXXVII



XXXVIII

In XXXVI, decomposition to 4-nitro-o-xylene involves loss of DOAc, whereas in XXXVIII loss of HOAc occurs. If loss of DOAc were slower than loss of HOAc, then some of XXXVI might decompose by the alternative loss of HNO_2; more of the resultant 4-nitro-o-xylene would then arise from XXXVIII than from XXXVI. 4-Nitro-o-xylene from 4-deutero-o-xylene would therefore contain more than the statistical (50%) amount of deuterium. The same reasoning applies to XXXV and XXXVII; the 3-nitro-o-xylene from 3-deutero-o-xylene would contain more than 50% deuterium. An isotope effect in normal electrophilic nitration, on the other hand, has never been observed except in the special, highly hindered case of 1-substituted-2,4,6-tri-t-butylbenzenes[28].

Accordingly, the products of nitration of 3- and 4-deutero-o-xylenes were separated and analyzed for deuterium content. The results (Tables XXIV-XXVII) show that within the errors of the mass spectrometric analysis, 50% deuterium is left in the nitroaromatics. This is some confirmation that the formation of nitro- products is a normal electrophilic substitution. It is not conclusive, however, since decomposition of the deuterated dienes could proceed without a sufficiently large isotope effect to produce an observable difference.

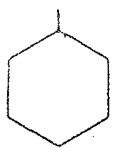
Conclusion

The formation of acetoxy products from methylbenzenes in nitric acid-acetic anhydride takes place through nitration at an alkylated ring position followed by addition of acetate to give 1,4-diene adducts which eliminate HNO_2 to give the acetoxy products. Alternatively, if the diene formed has a good leaving group like bromine geminal to the acetate group, elimination of acetyl bromide and formation of a cyclohexa-2,5-dienone will occur, leading eventually to nitro-phenol products. A further alternative reaction, either of the diene or of the carbonium ion precursor to the diene, leads to 4-methylenecyclohexa-2,5-diene intermediates, and hence to side-chain nitration. The nature of the nitrating agent in the first step is still not clear, but evidence is consistent with it being NO_2^+.

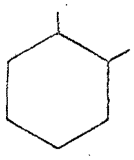
APPENDIX

Trivial Names of Polymethylbenzenes

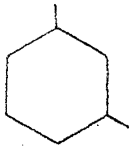
Methyl groups are represented by lines, and aromatic π-bonds are not shown.



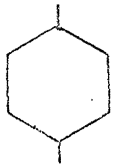
toluene



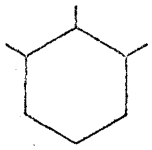
o-xylene



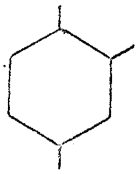
m-xylene



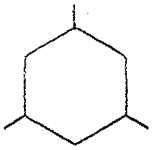
p-xylene



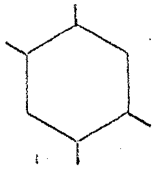
hemimellitene



pseudocumene



mesitylene



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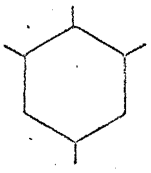

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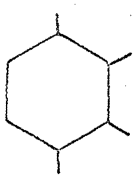
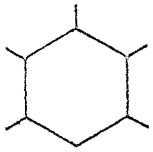
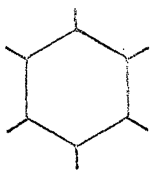


prehnitene



penta-
methylbenzene



hexa-
methylbenzene

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